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MARCH, 1943

BRAIN

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STUDIES OF NEUROMUSCULAR DISORDERS: THE MYOGRAM, BLOOD CHOLINESTERASE AND EFFECT OF PROSTIGMINE IN MYASTHENIA GRAVIS AND PROGRESSIVE MUSCULAR ATROPHY.[1]

BY GUY ODOM, COLIN K. RUSSEL AND DONALD McEACHERN.

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[1] From the Department of Neurology and Neurosurgery, McGill University, and The Montreal Neurological Institute, Montreal.

(1) Introduction.

It appears to be established that acetylcholine plays an important and perhaps essential role in the transmission of nerve impulses to voluntary muscle. Dale, Feldberg and Vogt (1936) have shown that acetylcholine is liberated at motor nerve endings when the nerve is stimulated. None is liberated on stimulation of a degenerated nerve although the muscle still contracts when acetylcholine is injected into its artery. It seems that nerve impulses cause acetylcholine to be exploded in close proximity to the muscle cell, and that this substance fires off the normal machinery for contraction. An enzyme, cholinesterase, present both in tissue and blood, rapidly destroys acetylcholine, prevents its spread to adjacent muscle fibres and thus localizes and controls the duration of its action. Physostigmine and its analogue, prostigmine, act by inhibiting cholinesterase and thus delay the destruction of acetylcholine. They serve, therefore, to potentiate acetylcholine effects. Curare does not prevent formation of acetylcholine nor does it paralyse the muscle directly, but it seems to act as a barrier between nerve ending and muscle fibre, and muscular contraction is then feeble or absent when the nerve is stimulated.

There has naturally been an attempt by numerous workers to apply the newer knowledge of chemical transmission to the neuromuscular diseases (Gammon, Masland and Harvey, 1941; McEachern, 1942). Most attention has been focused on myasthenia gravis. Kennedy and Wolf (1937) have suggested that myasthenia gravis involves defective chemical transmission and that myotonia may result from an over-effective mechanism. They have pointed out that the two conditions may be clinical opposites. The present work was done in order to study the chemical and myographic abnormalities of myasthenia gravis and to compare them with similar studies in cases of progressive muscular atrophy. A brief abstract of this work has appeared previously (Russel, Odom and McEachern, 1938).

(2) Material and Methods.

Clinical Material.

Eleven cases of myasthenia gravis were studied. The patients varied in age from 13 to 67. Six were males and five were females. Onset of symptoms occurred in the two youngest patients at the ages of 11 and 15 years respectively. Prostigmine caused definite improvement of symptoms in all patients.

The diagnosis was usually simple on the basis of classical signs and symptoms, but in several instances it depended on the myograms or prostig-

mine tests. The following cases are presented in summary because of certain unusual features:—

Case 1.—W. P., male, aged 67. Onset with diplopia following attack of influenza. Five months later—ptosis of eyelids, deficient movements of eyeballs, weakness of palate and general musculature. Pupils small and inactive to light. Moderate vascular hypertension and considerable arteriosclerosis. *Note:* (*a*) The distribution and constancy of symptoms at first suggested mesencephalitis hæmorrhagica. The myogram showed a typical myasthenic defect, however, and prostigmine caused considerable amelioration of symptoms. (*b*) During bouts of urinary retention due to prostatic obstruction there was a marked increase of myasthenic symptoms. (*c*) It was not possible to relieve the symptoms entirely or correct the myogram completely even when 2·5 mgm. prostigmine were given intramuscularly or when 15 mgm. were given by mouth twelve times in twenty-four hours. Choking and dyspnœa often threatened the patient despite the latter dosage.

Case 2.—B. B., female, aged 18. Onset four months previously with sudden spells of weakness in legs which caused numerous falls. This was followed by progressive weakness of trunk and limb muscles. She was unable to sit up without the aid of her arms and rose from a horizontal position on the floor in the way characteristic of muscular dystrophy. Examination was otherwise negative and there was no muscular hypertrophy nor evidence of extra-ocular or bulbar involvement. *Note*: The tentative diagnosis was progressive muscular dystrophy. The myogram showed a typical myasthenic abnormality and intramuscular prostigmine caused rapid return of muscle power. Only several weeks later did temporary mild diplopia, ptosis and weakness of jaw and palate complete the clinical picture. The patient has returned to her work as a typist and symptoms are well controlled by oral prostigmine, 15 mgm. t.i.d.

Case 3.—G. B., male, aged 24. Onset with diplopia six months previously. Examination showed marked ptosis of left upper eyelid and limitation of all movements of left eyeball save medially. No other signs or symptoms of myasthenia were present. *Note:* The myogram was normal but prostigmine caused rapid clearing of the ptosis and diplopia. His general muscular endurance also increased markedly although he had not previously been aware of undue fatigability.

Case 4.—R. S., male, aged 13. Onset six months previously with weakness of palate, face and jaws, followed by ptosis of eyelids and general fatigability. He had been treated for bronchial asthma and allergy for several years. Questioning revealed, however, that dyspnœa and wheezing respiration had only occurred during severe muscular effort and that the symptoms disappeared after ten minutes of rest. *Note:* (*a*) The "asthmatic" attacks were probably early respiratory symptoms of his myasthenia. (*b*) Small amounts of prostigmine (0·5 mgm.) intramuscularly were more effective than larger doses (2 mgm.) in controlling symptoms and correcting the myographic defect. The larger doses actually increased this defect although a satisfactory fall of serum cholinesterase occurred.

Six cases of progressive muscular atrophy were studied. There was sufficient evidence of involvement of the cortico-spinal tracts in three cases to permit their classification as amyotrophic lateral sclerosis. Four patients were males and two were females and their ages varied from 38 to 61 years. Fasciculation or some degree of muscular atrophy were present in all.

A number of normal individuals and patients with diseases unrelated

to those discussed in this paper were studied as controls. In addition there was a patient with muscular dystrophy and another with familial periodic paralysis (Pudenz, McIntosh and McEachern, 1938). Myograms were made on two patients with chronic thyrotoxic myopathy (McEachern and Ross, 1942).

Myograms.

Myograms were recorded from the little finger and registered with a spring myograph upon a smoked drum during stimulation of the motor point of the ulnar nerve about 4 cm. above the internal condyle of the humerus. The forearm and hand were immobilized in a metal splint and the interphalangeal joints of the free fifth finger were kept rigid by means of light aluminium splints. The indifferent electrode was placed on the opposite arm.

The stimulator was designed for us by our colleague Dr. A. Cipriani and is a modification of that described by Hill (1934). A condenser of 0·5μ F. capacity is charged by dry cells to a maximum potential of 36 volts and a 100 ohm voltage divider permits stimulation at lower voltages and allows the condenser to be fully discharged even at the highest frequencies. A rotating commutator connected as a charge and discharge switch is driven at varying speeds and results in discharges at frequencies of from 20 to 840 per second. The frequencies are read in terms of voltage produced by a small generator placed at one end of the revolving shaft, calibration having been made with a cathode ray oscillograph.

Stimulation was carried out at eleven different frequencies ranging from 34 to 840 per second. Each stimulus was maintained for two or three seconds with rest periods of about fifteen seconds intervening.

Cholinesterase.

Cholinesterase was determined by Miss Doris Brophy in serum and defibrinated blood by Ammon's method (1933). Venous blood was defibrinated with a glass rod and diluted 1:50 with bicarbonate Ringers[1], a similar dilution being used for serum. 1·5 c.c. of a 0·5 per cent. solution of acetylcholine chloride in bicarbonate Ringers was placed in the manometer flask and 0·5 c.c. of the blood or serum dilution in the side arm. Estimations were carried out at 37·5° C. under an atmosphere of 5 per cent. CO_2 in nitrogen and at pH 7·5. Cholinesterase activity is expressed as

[1] 100 parts 0·9% NaCl; 2 parts 1·15% KCl; 2 parts 1·22% $CaCl_2$; 20 parts 1·30% $NaHCO_3$; 4·3 parts 5·60% glucose.

cubic millimetre of CO_2 evolved in the sixty minutes following addition of blood or serum to the acetylcholine solution. In the charts, cubic millimetres of gas are expressed as units for the sake of simplicity. A small degree of auto-hydrolysis of acetylcholine occurred and this was measured in each experiment and subtracted from the figures of cholinesterase activity. Determinations repeated on blood and serum kept for twenty-four hours in the refrigerator showed only a small reduction (about 10 per cent.) of cholinesterase activity after this interval. After prostigmine, all determinations were made on blood drawn one hour after intramuscular injection of the drug, unless otherwise stated.

(3) Results.

Myasthenia Gravis.

Myograms.—Normal individuals respond with sustained contraction at any rate of stimulation between 34 and 840 shocks per second (fig. 1).

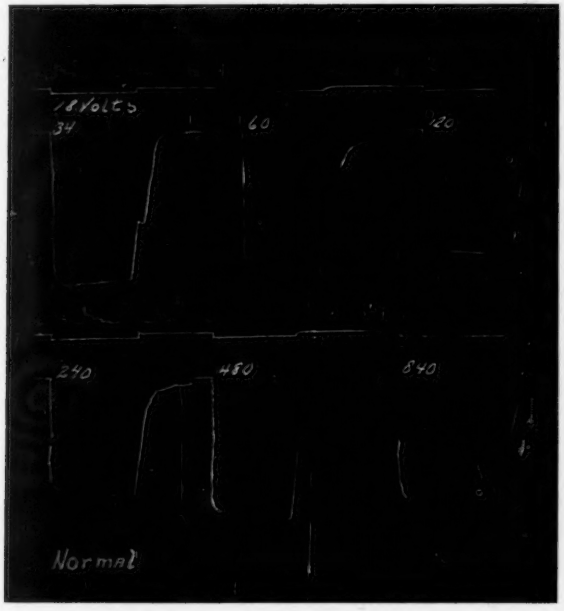

Fig. 1.—Normal myogram. In this and succeeding tracings there are shown from above downwards: Time signal in seconds; stimulation signal; myogram.

In nine of the eleven patients with myasthenia gravis an abnormality was found which appears to be characteristic of this disease and which was first described by Pritchard (1933, 1935). It (fig. 2) seemed identical in

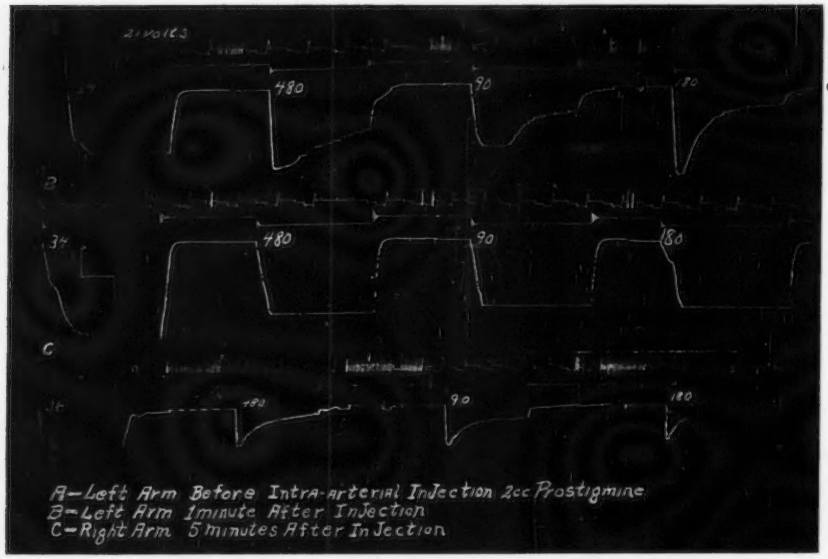

FIG. 2.—Myogram in myasthenia gravis. See text for details.

form, although not perhaps in mechanism, with the phenomenon of Wedensky inhibition known to the physiologist, and with the twitch-like response of curare poisoning in animals (1936).

At low rates of stimulation the contraction was maintained as in normal individuals. At rates above 90 per second contraction was not maintained, and in severe cases it was twitch-like, the curve falling away at once towards the base line despite continuance of the stimulation. This defect was usually greatest at rates of stimulation between 90 and 180 per second. Myasthenics also showed poor height of contraction and higher voltage was necessary to obtain good records. The patients were often not aware of any weakness or fatigability in the hands although records revealed this defect. In Case 1, the record was of diagnostic help. In Case 2, the correct diagnosis had not been considered until the myogram was obtained. In other cases the myograms were useful in studying the effect of therapy. Normal myograms were obtained from two patients, both of

whom showed delimited bulbar or ocular signs. They suffered no undue fatigability of trunk or limbs.

Site and mechanism of prostigmine effect.—In myasthenics, following prostigmine[1], the height of the contraction was greater and the myogram returned to normal—that is, the contraction was sustained at high rates of stimulation as well as at low. Complete return to a normal myogram occurred about forty-five minutes after intramuscular injection of an adequate dose of prostigmine. The defect reappeared in the myogram later while the patient could still feel the full benefit of the drug. In the two most severe cases the defect in the myogram could not be completely corrected, although varying doses of prostigmine (up to 2·5 mgm.) were used and the patients enjoyed marked clinical improvement.

In an attempt to localize the action of prostigmine it was injected into the left brachial artery while venous return from the limb was blocked with a blood-pressure cuff. The myogram of the injected limb returned to normal within one minute or less (fig. 2*b*) while the tracing from the opposite limb still showed the abnormality (fig. 2*c*). The cuff was then deflated and blood from the injected limb was allowed to enter the general circulation. Several minutes later generalized improvement of symptoms set in. The myogram of the injected limb was still normal after one hour (fig. 3*a*), but that of the uninjected limb never became normal (fig. 3*b*)

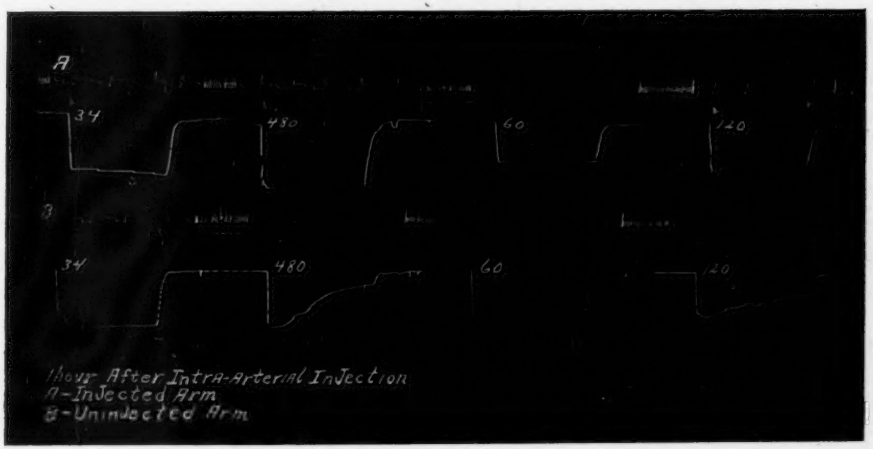

FIG. 3.—Myogram in myasthenia gravis. See text.

[1]We are indebted to Hoffmann-La Roche Limited for generous supplies of prostigmine methyl sulphate.

because of the inadequate amount of prostigmine reaching it after removal of the venous tourniquet from the injected limb. These results give objective confirmation to the findings of Fraser, McGeorge and Murphy (1937) and of Lanari (1938).

An interesting comparison can be made between the myogram (fig. 3) and the blood cholinesterase (fig. 4) following intra-arterial prostigmine.

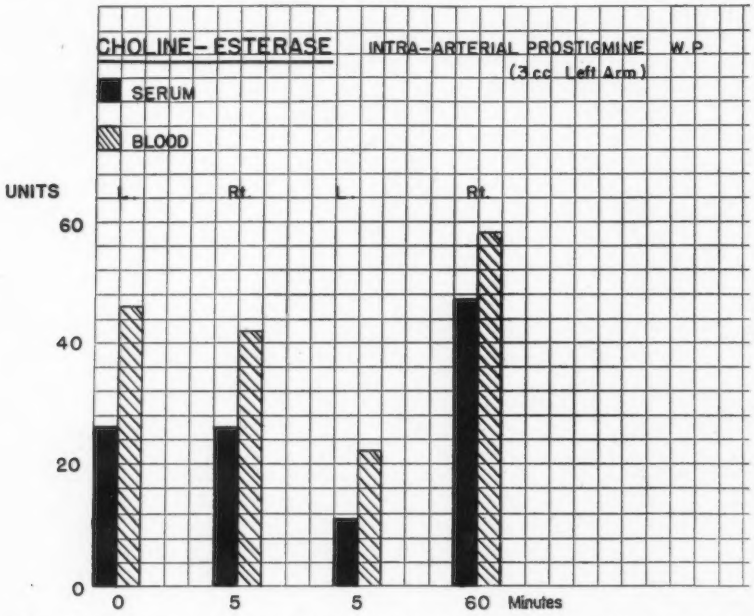

FIG. 4.—Example of effect of intra-arterial injection of prostigmine on blood cholinesterase in myasthenic patient. See text.

After one hour the myogram from the injected limb was still normal, whereas the cholinesterase of circulating blood had risen above the level which existed before injection of prostigmine. This indicates that the persisting effect of the drug is upon the muscles of the injected limb and that the level of cholinesterase in the circulating blood is not the essential factor.

In one patient whose myogram remained abnormal, even after 2·5 mgm. prostigmine intramuscularly, the defect disappeared at once in the injected limb after intra-arterial prostigmine. We conclude not only that the

beneficial action of prostigmine is a peripheral effect, but that the reduction of *muscle* cholinesterase is the essential factor.

Two patients with chronic thyrotoxic myopathy (McEachern and Ross, 1942) had marked muscular fatigability. Their myograms showed the myasthenic defect and this responded to prostigmine.

Blood cholinesterase.—The serum cholinesterase is remarkably constant from day to day in a given normal individual, but there is considerable variation of the basal level in different people (fig. 5). The cholin-

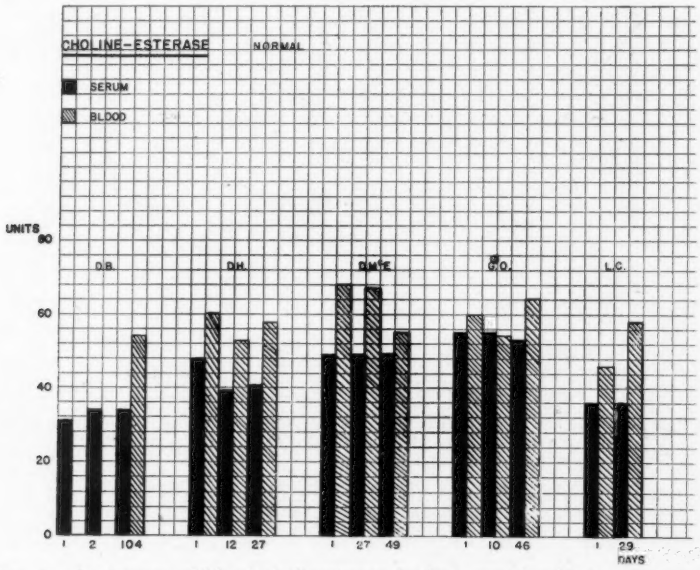

FIG. 5.—Variations of blood cholinesterase in five normal subjects over a period of time.

esterase of defibrinated blood is usually somewhat higher than that of serum, due to the greater cholinesterase activity of the corpuscles, as shown by Stedman and Russel (1937). It is also more variable from day to day in normal individuals and patients. In the myasthenic patient the variation of blood cholinesterase, over a period of time, is no greater and the level falls within the wide limits of normal (fig. 6). Thus there is no evidence that myasthenia is due to increased destruction of the chemical transmitter by an abnormally high cholinesterase activity of blood. Increased activity might, of course, be present in the muscle cholinesterase. The only two

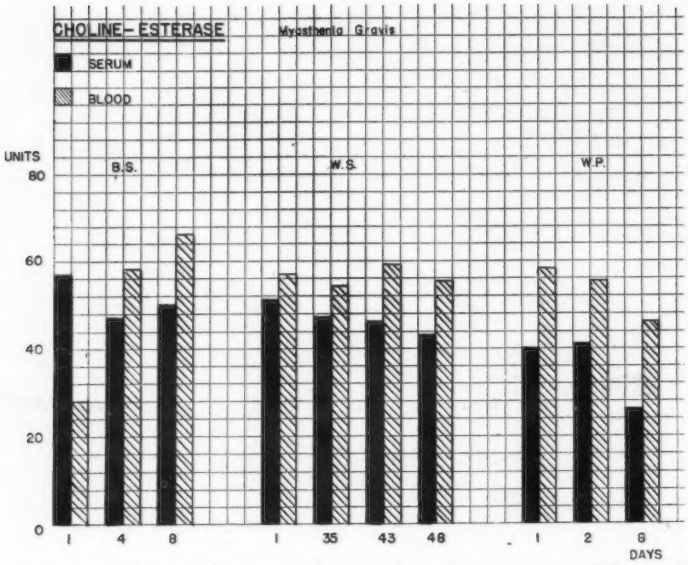

FIG. 6.—Variations of blood cholinesterase in three patients with myasthenia gravis over a period of time.

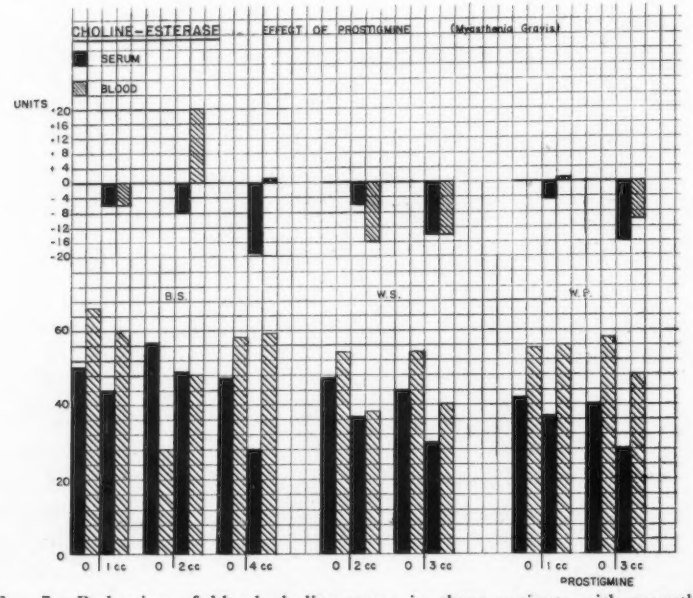

FIG. 7.—Reduction of blood cholinesterase in three patients with myasthenia gravis following various doses of prostigmine intramuscularly.

determinations available on myasthenic muscle have shown no abnormality (Jones and Stadie, 1939; Goodman, Carlson and Gilman, 1939).

Prostigmine causes a marked fall of serum cholinesterase which is so constant for a given individual that it can be said to parallel the dose of the drug (fig. 7). This drop corresponds with the period of clinical improvement. A similar fall of cholinesterase follows prostigmine in cases other than myasthenia gravis, and in normal individuals too. The response of the cholinesterase of defibrinated blood is more variable (fig. 7).

Progressive Muscular Atrophy.

Myograms and blood cholinesterase.—Patients with progressive muscular atrophy showed normal myograms inasmuch as contraction was maintained at all frequencies of stimulation. Many irregular twitches appeared, however, due to fasciculations. The latter were visibly increased in a muscle during mild stimulation of its nerve (e.g. 5 to 10 volts). They disappeared from the records when the strength of the stimulus was increased, probably because more powerful contraction of the normal muscle fibres covered them up. No abnormality could be detected in the patient with myopathy nor in the boy with familial periodic paralysis during partial or complete recovery from attacks.

Cholinesterase in serum and whole blood was found to be within normal limits in the six patients with progressive muscular atrophy. There was therefore no evidence that peripheral chemical transmission might be enhanced due to reduction of circulating cholinesterase. Prostigmine caused a reduction of blood cholinesterase similar to that found in myasthenics and normal individuals. During the time of action of the drug fasciculations appeared or were greatly intensified.

Mechanism of fasciculation.—In three patients with progressive muscular atrophy who had spontaneous fasciculation in the anterior tibial group of muscles, the common peroneal nerve was injected with 1 per cent. novocain which produced a complete nerve block. After the injection there was sensory loss and complete motor paralysis of the area supplied by the nerve. There was also no response to strong electrical stimulation applied above the site of the block. In one case a needle electrode was inserted into the nerve and stimulation demonstrated the completeness of the block. In all three cases the fasciculation persisted in the anterior muscles with the same intensity. A similar result was obtained in one patient with fasciculation due to chronic thyrotoxic myopathy.

Intramuscular (deltoid) injection of prostigmine increased the fascicula-

tion in the anterior tibial muscles and elsewhere throughout the body. We conclude that this fasciculation was of peripheral origin and not due to disordered impulses coming down from the anterior horn cells.

In two other cases nerve block caused fasciculation to disappear from the anterior tibial muscles. In both instances the twitchings had only been elicited previously by posturing the limb. It would seem that in these patients the mechanism was a different one or, more likely, that the fasciculation was only brought about by tonic impulses descending from the anterior horn cells when the limb was postured.

Effect of prostigmine.—In all of these cases intramuscular injection of 1 mgm. prostigmine markedly increased the spontaneous fasciculation and also caused it to develop in previously unaffected muscles. Brisk fasciculation was apt to appear almost at once in a small area surrounding the point of injection. Two patients showed spontaneous fasciculation only when the limbs were postured, but after prostigmine fasciculation was present when the limbs were at rest. It may appear in normal individuals following large doses, but we have never observed it in patients with myasthenia gravis even after doses of 2·5 mgm. The patient with myopathy showed no fasciculation following injection of 2 mgm. prostigmine.

The readiness with which small doses of the drug produce fasciculation in muscles subject to motor neurone degeneration has led us to use prostigmine as a therapeutic test. We have noted the appearance of fasciculation in affected muscles in two cases of progressive muscular atrophy after injection of as little as 0·5 mgm. prostigmine, whereas it was not previously present.

Prostigmine fasciculation in animals.—Prostigmine causes marked generalized fasciculation in animals. In repeating some of the experiments performed many years ago by Langley and Kato (1915) with physostigmine we have found that these fasciculations persist after section of the spinal cord and of all the nerves to a limb. They persist in an amputated limb and in the body for upward of twenty minutes after death of the animal. Langley and Kato found that eserine failed to produce fasciculation about twenty-nine hours after motor nerve section and that this lack of response persisted until the fifth day. We have confirmed this observation using prostigmine. Atropine has no effect on the fasciculation. It was possible, however, to abolish the twitching at once by intravenous injection of curare in amounts so small as to cause no apparent decrease in the muscle power or activity of the animal. Rabbits and cats were used in these experiments. An attempt was made to determine whether prolonged fasciculation due

to prostigmine would cause muscular atrophy. Prostigmine 0·5 mgm., together with atropine 0·1 mgm., was injected subcutaneously twice a day for a period of three months into a number of white rats. Fasciculation was brisk, but only persisted for a total of about two hours during each twenty-four hours. No gross or microscopical abnormality was observed in the muscle fibres or motor end plates. This test was obviously inadequate.

(4) Discussion.

Since Walker (1934, 1935) discovered the remedial effect of physostigmine and prostigmine in myasthenia gravis the natural tendency has been to suspect a fault of neuromuscular transmission involving acetylcholine. It was at first thought that an excessive activity of the blood cholinesterase might cause accelerated breakdown of acetylcholine at the site of its liberation. Our studies and the results of others (Masland and Wigton, 1940; Milhorat, 1938; Stedman and Russel, 1937) eliminate this possibility. Indeed, the absence of signs of deficient cholinergic activity in visceral organs (heart, bowel, bladder, &c.) in this disease are clinical points against the theory.

Overactivity of tissue esterase at the neuromuscular junction might of course be present and our results with intra-arterial prostigmine indicate that the peripheral fault may be controlled while blood cholinesterase is normal. Estimations of muscle cholinesterase in two instances (Goodman, Carlson and Gilman, 1939; Jones and Stadie, 1939) have not shown any abnormality, however, and the beneficial effect of prostigmine can be explained on grounds other than the overcoming of an *excessive* concentration of tissue cholinesterase. We are impressed with the fact that some severe cases fail to improve beyond a certain point even with large doses of prostigmine; indeed, small doses are sometimes more effective than large doses. This would indicate that the cholinergic transmission can only be potentiated to a certain extent with prostigmine and that the inherent defect may remain. There is a parallel in the work of Briscoe (1936), who found that prostigmine could remedy the myographic defect due to curare in animals if curare was not given in too large amount. Prostigmine, even in high dosage, did not overcome the defect due to large amounts of curare; indeed, there were super-added signs of prostigmine poisoning. Walker (1938) noted, in a patient with myasthenia gravis, increased weakness of the extra-ocular and other muscles upon removal of a tourniquet from a limb that had been exercised. She attributed this to the release of a

curare-like substance from the fatigued muscles. Although we think that this observation might be explained on other grounds, e.g. the release of lactic acid or other metabolites, we feel that a curare-like substance should be sought for in this disease. The similarity of myasthenia gravis to the symptoms of curare poisoning in man is striking.

Others have suggested that abnormally small amounts of acetylcholine may be liberated at the neuromuscular junction in this disease. There is no proof as yet for this, although the experiments of Fraser, McGeorge and Murphy (1937) are suggestive. These workers injected choline esters and reported more prolonged recovery than that due to prostigmine. This work has not been confirmed by others (Gammon, Masland and Harvey, 1941).

The effect of prostigmine in normal individuals and in patients with progressive muscular atrophy makes one give thought to the mechanism of muscular fasciculation. Denny-Brown and Pennybacker (1938) have recently illuminated this subject in their excellent paper. We presume, as they did, that fasciculation in this disease is due to enhanced irritability of the myo-neural junction or the muscle fibre to acetylcholine, a phenomenon which is well known to follow denervation of muscle, e.g. destruction of anterior horn cells or motor nerve fibres.

Attention should be paid, however, to the possibility that peripheral enhancement of the cholinergic transmitting mechanism may be the primary fault, whereas anterior horn cells and corticospinal tract damage may be secondary phenomena. The following points come to mind in this regard: (*a*) Muscular fasciculation and tendency to cramps may be marked and generalized long before any atrophy is evident. (*b*) Fatigability may far exceed the evidences of muscle atrophy. (*c*) Complete denervation of muscle in man, such as by traumatic nerve section, causes very fine, almost invisible fibrillation, but not fasciculation. (*d*) Patients with chronic thyrotoxic myopathy may show marked fasciculation without evidence of organic motor neurone disease.

A finding of Denny-Brown and Pennybacker (1938) is also of interest in this connection. These workers were able to record the electrical discharges from a motor unit during fasciculation associated with motor neurone disease. The same motor neurone was shown to be capable of discharging a normal series of nerve impulses in response to the willed effort of the subject. If the fasciculation is to be attributed to denervation it is hard to see how a normal willed impulse can be conducted to the muscle fibres. The fine fibrillation which Langley and Kato (1915) described and

the sensitization of the muscle to acetylcholine both make their appearance some days after complete section of the motor nerve fibres.

Masland and Wigton (1940) have shown that prostigmine fasciculations cause an antidromic volley of impulses to course from the periphery up the motor nerve fibres. Presumably the same thing occurs with spontaneous fasciculation associated with motor neurone disease. What effect such bombardment might ultimately have on the anterior horn cells is not known.

It can certainly be said that some instances of generalized fasciculation are not associated with motor neurone disease. We recently examined a middle-aged man who was turned down for the Army because of "abnormal heart sounds." These were found to be due to coarse fasciculations of the intercostal muscles which made a rat-tat sound in the stethoscope. Generalized twitchings were found in the musculature elsewhere. They were known to have been present for twenty-two years. There was no sign of muscular wasting or disease of the nervous system. Another instance can be cited of a young surgeon subject to generalized fasciculations for at least seven years, especially when smoking heavily. Examination showed coarse, generalized fasciculation with no evidence of neurological disease. No twitching could be found a week later, during which period he had not smoked.

We would therefore suggest the possibility that fasciculation may in some instances be due to over-activity of the cholinergic transmission system rather than to sensitization resulting from primary degeneration of the motor neurones.

Two of our cases of progressive muscular atrophy had florid, generalized fasciculations, muscular cramps and no evidence of corticospinal tract involvement. Death occurred a few months after the onset of symptoms. It is tempting to think of such cases as perhaps associated with a disordered or too free release of acetylcholine at motor nerve endings. The picture was almost identical with the transient neuromuscular effects of prostigmine over-dosage in normal individuals. The latter is characterized by gross muscular spasms and fasciculations rather than by simple myotonia. There is no proof that such a mechanism operates in progressive muscular atrophy, but the idea serves as an interesting speculation for those working in this field.

(5) Conclusions.

(1) Myograms from patients with myasthenia gravis show a characteristic abnormality at high rates of stimulation of the motor nerve.

(2) The myogram becomes normal within forty-five minutes after intramuscular injection of prostigmine, and almost at once in the injected limb when the drug is given intra-arterially. The action of prostigmine is peripheral.

(3) In a limb which has been injected intra-arterially with prostigmine the myogram remains normal after the cholinesterase of circulating blood has risen to the pre-injection level or above it. The persisting benefit in the limb must therefore be due to the lowering of muscle cholinesterase.

(4) The cholinesterase of serum and of defibrinated blood was not abnormal in patients with myasthenia gravis or progressive muscular atrophy. In each individual studied prostigmine caused a fall of serum cholinesterase which paralleled the dose. The effect of defibrinated blood was more variable.

(5) In three cases of progressive muscular atrophy fasciculation persisted in muscles after the motor nerve fibres had been blocked with novocain. The fasciculation was therefore of peripheral origin and not due to aberrant impulses from anterior horn cells. It is suggested that degeneration of the motor neurone sensitizes the muscle to normal amounts of acetylcholine or that in some instances there may be an excess of the chemical transmitter.

(6) In patients with progressive muscular atrophy a small dose of prostigmine (0·5 to 1 c.c.) brings on or intensifies fasciculation. Normal individuals and myasthenics do not fasciculate with such doses.

(7) Mention is made of prostigmine fasciculation in animals and man. This is of peripheral origin. In animals this fasciculation disappeared after doses of curare which did not seem to affect muscle power or activity.

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SUBDURAL EMPYEMA.

BY CHARLES S. KUBIK[1] AND RAYMOND D. ADAMS.[2]

SUBDURAL empyema or abscess is generally regarded as a rare condition which is indistinguishable clinically from other forms of intracranial suppuration, notably brain abscess, sinus thrombophlebitis or meningitis. In this review of fourteen cases, twelve with post-mortem examinations and two in which recovery followed surgical treatment, the clinical features were found to constitute a fairly definite syndrome, the recognition of which should, in our opinion, lead to earlier diagnosis and more effective treatment.

The term *subdural empyema,* or *subdural abscess,* denotes a collection of pus between the dura and arachnoid. Various names have been applied to it, such as cortical abscess (Bleguard and Mygind), circumscript meningitis (Lemoyez), internal purulent pachymeningitis (Blegvad), intrapia-arachnoid abscess (Eagleston), and phlegmonous meningitis (Witzel). Most of these terms are objectionable for obvious reasons, and *abscess* is not strictly appropriate because a collection of pus in a preformed space is not an abscess but an empyema. We have, therefore, adopted the latter term.

HISTORICAL NOTE.

The first recorded observation of subdural empyema was published in 1886 by Ceci and Onetti (1889) of the Surgical Clinic of Geneva. A few years later MacEwen (1893) in his monograph, "Pyogenic Infections of the Brain and Spinal Cord," reported four cases but only gave meagre clinical data. Subsequently subdural empyema became generally recognized as a pathological entity through the writings of Jansen and Delstanche (1895), Korner (1908), and Heine (1903).

In 1919, Blegvad (1910) was able to collect forty-four cases, and his ideas on the subject were accepted as authoritative by subsequent writers for the next two decades. He stated that chronic suppuration of the ear was usually the source of the infection, which entered the subdural space either by direct extension or as a consequence of thrombophlebitis. Although the

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symptoms were described, clinical differentiation between subdural empyema and cerebral abscess was considered impossible. Surgical drainage was the treatment recommended.

The literature was reviewed again by Reudi (1930), who arrived at essentially the same conclusions as Blegvad. Hecquet (1934) made notable contribution to the subject by formulating a clinical syndrome. He believed that the coexistence of certain signs and their order of appearance in the course of the rapidly evolving infection made diagnosis possible. He gave as the essential features chronic or, more rarely, an acute infection of the tympanic cavity, signs of systemic infection and, following in fairly rapid order, signs of meningeal irritation, increased intracranial pressure and focal manifestations of cerebral involvement. Isolated case reports of otogenic subdural empyema by Butler (1912), Post and Mollison (1926), Liebermann and Petzal (1926), Tobl (1929), Hens (1930), Meyer (1933), Geschelin (1931), Fernando and Ayuyao (1933). and Gardner (1933), have served to elucidate certain details of the clinical or pathological picture.

A circumstance for which we have discovered no adequate explanation is the preponderance of ear infections as the source for the subdural empyema in all the aforementioned papers. Very few cases complicating sinusitis had been reported until the recent communications of MacGregor and Smith (1935), Geraghty (1936), Courville (1936), and Courville and Nielsen (1934).

Metastatic infection of the subdural space in the course of septicæmia has been reported only once, by Clifton and Werner (1938).

Case Reports.

The fourteen cases of subdural empyema on which this report is based were observed during the past four years in the wards of the Massachusetts General Hospital and the Massachusetts Eye and Ear Infirmary. Of this number twelve followed paranasal sinus infection, one was secondary to ear infection, and one, metastatic in origin, was secondary to chronic pulmonary suppuration. Twelve died and two, both resulting from sinus infection, recovered. Post-mortem examinations were made in all of the fatal cases.

Case 1.—Male, aged 22. *History:* For several months the patient's nose had been "stopped up" and he had been blowing pus and blood from it. Then, two days after he had been swimming he complained of severe pain over his left eye, was feverish, and vomited. On the next two days the headache became generalized and steadily increased in severity. On the fourth day of his illness, a few hours

before he entered the hospital, he became confused and irrational and lost the ability to speak.

Examination.—Temperature 105° F.; pulse 80; respiration 20; blood-pressure 150/70.

The patient was restless and stuporous. There was orbital swelling, slight proptosis on the left side and tenderness over both frontal sinuses. The patient was unable to speak but understood what was said to him. His neck was moderately stiff. Visual fields were full by rough confrontation tests and optic fundi were normal. The eyes deviated spontaneously to the left, and there was paralysis of lateral conjugate movement to the right. There was a right-sided hemiparesis involving the face, arm and leg. Response to pain stimuli was equal on the two sides of the body; more accurate sensory tests could not be done. The tendon reflexes were more active on the right side, abdominal reflexes were absent, and no plantar reflexes could be elicited.

Laboratory data.—White blood cells 10,800, 82 per cent. polymorphonuclear leucocytes. Cerebrospinal fluid: Pressure 165 mm.; cells 40 per c.mm., 8 per cent. polymorphonuclear leucocytes; total protein 108 mgm. per cent.; sugar 93 mgm. per cent.; chloride 655 mgm. per cent.; Lange reaction 0012331100. X-ray examination disclosed only " slight thickening of mucous membrane of right antrum."

Course.—Under treatment with sulfapyridine the patient's condition grew worse and by the morning of the fifth day of his illness he had become comatose. A radical, bilateral frontal, left ethmoid and left sphenoid sinus operation was then performed. The left frontal sinus contained thin, yellow pus. No osteomyelitis was found. The dura on being exposed was thought to be normal and was not opened. Death occurred a few hours later, on the fifth day of the illness and one day after the onset of focal signs.

Pathological findings.—Subdural empyema, left, without organization. Acute suppurative sinusitis, left frontal. Thrombophlebitis of superior longitudinal sinus. Thrombosis of subarachnoid veins. Localized acute meningitis. Necrosis of cerebral cortex and subcortical white matter.

Comment.—Thrombosed veins, foci of suppuration and hæmorrhages were observed in the dura and falx overlying the subdural exudate. There were no hæmorrhages in the cortex. No disease of the bone or dura over the paranasal sinuses was demonstrated, and it seemed reasonably certain that the infection had extended to the subdural space from the superior longitudinal sinus.

Case 2.—Male, aged 55. *History:* For many years the patient had had chronic sinusitis and bronchiectasis. Four months before admission there had been an exacerbation of the sinus infection with pain over the sinuses and purulent nasal discharge. A bilateral Caldwell-Luc operation and intranasal ethmoidectomy were performed. Just as he was about to be discharged from the hospital on the eleventh post-operative day he developed fever and right orbital swelling. These symptoms continued. X-ray examination on the nineteenth post-operative day disclosed pansinusitis and osteomyelitis of the lower rim of the right orbit. Two days later an orbital abscess was incised and drained. The temperature dropped to normal, remained so for five days, and then became elevated again. Sulfanilamide was given, but the patient did not improve and twenty-two days after the onset of orbital swelling a series of left-sided convulsions occurred.

Examination.—Temperature 103° F.; pulse 105; respiration 30.

The convulsions began on the left side of the body, the eyes and head first turning to the left, and became generalized. Between seizures the patient was stuporous and had a left hemiplegia. No observations of optic fundi, ocular movements or visual fields were recorded.

Laboratory data.—White blood cells 19,000. Cerebrospinal fluid: Pressure 160 mm.; cells 140, 80 per cent. polymorphonuclear leucocytes; total protein 118 mgm. per cent.

Course.—Sulfapyridine was given. On the following day a trephine was made above and slightly anterior to the right ear; there was no pus directly beneath the craniotomy, but on exploring a considerable quantity of subdural pus was encountered further anteriorly. The patient remained comatose, continued to have left-sided Jacksonian convulsions and died thirty-six hours later, or two and a half days after the onset of focal signs.

Pathological findings.—Subdural empyema, right, with organization. Acute suppurative pansinusitis. Osteomyelitis of right frontal bone. Epidural granulations, right frontal region. Thrombosis of subarachnoid veins. Localized acute meningitis. Necrosis of cerebral cortex. Orbital abscess, right. Temporal craniotomy, right.

Comment.—There was beginning organization in the outer (dural) layer of subdural exudate. A few of the subarachnoid veins contained very recent, bland, mural thrombi, none of which quite occluded the lumen. There was only slight, patchy necrosis of the cerebral cortex and no hæmorrhages. Venous sinuses were normal. Although no actual perforation of the bone or dura was demonstrated, it seemed reasonably certain that the epidural granulations represented the pathway-by which the infection extended from the right frontal sinus to the subdural space. It should be noted that the exploratory craniotomy was placed too far posteriorly.

Case 3.—Male, aged 37. *History:* There was a long history of frequent and protracted head colds and discomfort around the eyes. The present illness began two weeks before admission with swelling of the left eye and pain in the left frontal region, which continued for a week and was then followed by generalized headache. On the twelfth day of the illness there was a chill and high fever. Two days later the neck became stiff. Soon afterwards the patient lost the ability to speak and was brought to the hospital.

Examination.—Temperature 140° F.; pulse 68; respiration 20; blood-pressure 120/70.

The patient was stuporous. When aroused he could not talk or repeat what was said to him but understood spoken commands fairly well. His neck was stiff. There was orbital swelling, slight proptosis and tenderness over the frontal sinus on the left side. Optic fundi were normal. Visual fields were full by confrontation test. Pupils and pupillary reflexes were normal. The eyes deviated spontaneously to the left and could not be turned to the right. There was a right hemiparesis involving the face, arm and leg, with diminished tendon reflexes and an extensor plantar response on the affected side. Accurate sensory tests were not done, but pin-prick was felt equally well on the two sides.

Laboratory data.—White blood cells 29,500, polymorphonuclear leucocytes 80 per cent. Cerebrospinal fluid: Pressure 310 mm.; cells 427 per c.mm., 90 per cent. polymorphonuclear leucocytes; total protein 186 mgm. per cent.; Lange reaction 000012210. X-ray: "Haziness of the left frontal, ethmoid and maxillary sinuses. Normal aeration on the right. No evidence of osteomyelitis."

Course.—The hemiplegia persisted, the stupor deepened into coma and the patient died on the third hospital day, or seventeen days after the onset of the illness, nine to ten days after onset of generalized headache and two days after the appearance of focal neurological signs.

Pathological findings.—Subdural empyema, left, with slight extension to right side. Acute suppurative sinusitis, left, frontal and ethmoid. Necrosis and perforation of ethmoid bone and dura above left ethmoid cells. Thrombosis of subarachnoid veins. Localized acute meningitis. Necrosis of cerebral cortex and subcortical white matter.

Comment.—Direct communication, through overlying bone and dura, between ethmoid cells and subdural space was probably responsible for the infection. The superior longitudinal sinus contained a recent, infected mural thrombus at a point where the vessel wall was necrotic and infiltrated with polymorphonuclear leucocytes; this did not occlude the lumen and apparently was secondary to the subdural infection. The subdural exudate was not organized. There was dense infiltration of the inner layer of the dura with polymorphonuclear leucocytes.

Case 4.—Male, aged 14. *History:* This boy was admitted to the hospital because of fever, swelling of the left eye and headache. For the past several months he had been subject to frequent head colds. One week before admission he had a slight frontal headache. It was not severe, and he was sent that day to a boys' camp, where he went swimming soon after his arrival. On the following day the headache increased in severity and he had a chill. He was sent home and for the next five days had severe, continuous, generalized headache and several more chills. Then it was noted that he was less alert and responsive than usual and that the left eye was swollen. He was admitted to the hospital seven days after the onset of headache.

Examination.—Temperature 104° F.; pulse 120; respiration 22; blood-pressure 112/74.

He was an undernourished boy who was stuporous. There were orbital swelling and slight proptosis on the left side. Tenderness was noted over the frontal sinuses, more on the left. The neck was moderately stiff. Pupils were equal and reacted to light. There was paralysis of lateral conjugate movement of the eyes to the right and a right hemiplegia. All tendon reflexes were brisk, but those on the right side were more lively than the left. Abdominal reflexes were depressed bilaterally and extensor plantar responses were present on both sides.

Laboratory data.—White blood cells 16,900, 81 per cent. polymorphonuclear leucocytes. Cerebrospinal fluid: Pressure 350 mm.; cells 75 per c.mm., polymorphonuclear leucocytes 20 per cent.; total protein 108 mgm. per cent; chlorides 661 mgm. per cent.; sugar 113 mgm. per cent.; Lange reaction 0000122210. X-ray: "Diffuse thickening of mucosa of all the sinuses with obliteration of air cavities of left antrum and ethmoids. Acute pansinusitis with retained secretions on the left side."

Course.—On the second hospital day, or ninth day of illness, the patient became comatose and never again regained consciousness. The only treatment he received was sulfanilamide for two days after entry. He died on the fifth hospital day, or twelve days after the onset of his illness and six days after the appearance of focal neurological signs.

Pathological findings.—Subdural empyema, left. Acute suppurative pansinusitis, left, with probable necrosis of bone and dura above the posterior ethmoid cells. Thrombophlebitis of superior longitudinal and straight sinuses. Localized acute meningitis. Thrombosis of subarachnoid veins. Necrosis of cortex and subcortical white matter with small hæmorrhages in grey matter.

Comment.—It was not clear whether thrombophlebitis of the superior longitudinal sinus or direct extension from the ethmoid cells was responsible for the subdural infection. There was no organization of the subdural exudate. The inner layer of the dura was densely infiltrated with polymorphonuclear leucocytes. Considering the duration of symptoms and the absence of organization of subdural exudate, it is possible that the earlier symptoms of intracranial disease were due to the thrombophlebitis.

Case 5.—Male, aged 24. *History:* One month before the final hospital admission the patient had a plastic operation for a deformity of the nose. A post-operative hæmorrhage necessitated packing of the nose, following which the temperature rose to 104° F. and there was a bloody, purulent, nasal discharge. The fever subsided somewhat, but still rose to 101° F. at times when the patient left the hospital on the seventeenth post-operative day. Eight days after discharge and two days before readmission he had chills and left orbital pain which, on the following day, became a severe generalized headache.

Examination.—Temperature 106° F.; pulse 150; respiration 30; blood pressure 128/80.

There was stiffness of the neck, left orbital swelling and tenderness over the left frontal sinus. No neurological examination was recorded at this time.

Laboratory data.—White blood cells 15,000. Cerebrospinal fluid: (Third, fifth and seventh hospital days), the pressure was 280, 360 and 700 mm.; cells 360-910 per c.mm., 87 per cent. polymorphonuclear leucocytes; protein ranged from 102 to 156 mgm. per cent. and the sugar from 89 to 102 mgm. per cent.; cultures for bacteria were negative. X-ray: "Chronic bilateral ethmoid and antrum infections."

Course.—The left frontal sinus was opened but nothing abnormal was noted. On the third hospital day the posterior wall of the left frontal sinus was removed, disclosing what appeared to be normal dura. Following this procedure the patient continued to have severe headache and became less responsive. The pupils were dilated and reacted poorly to light. There was a complete left hemiplegia with increased tendon reflexes and Babinski sign on the left side. Cutaneous sensation was not impaired. Death occurred on the eighth hospital day, which was ten days after onset of generalized headaches and three to five days after the appearance of focal neurological signs.

Pathological findings.—Subdural empyema, right, with organization. Fracture (operative) of crista frontalis. Acute localized meningitis. Necrosis of cerebral cortex.

Comment.—The right frontal sinus was normal (the left was thought to be so at operation). There was pus in the sphenoid sinus, and the condition of the ethmoid cells (in which there was X-ray evidence of chronic inflammation) was not described. There was no thrombophlebitis of any of the venous sinuses. A fracture, measuring 1·2 cm. in length, was situated just above the foramen cæcum and extended across the crest of the cerebral surface of the frontal bone. The subdural exudate began over the right half of the fracture and, although no defect in the dura was observed, it seems likely that infection, possibly from the ethmoid cells, entered the subdural space through the fracture and overlying dura.

No thrombosed subarachnoid veins were observed but only a few small blocks of tissue were available for microscopic examination.

Case 6.—Male, aged 42. *History:* There had been no previous history of sinus infection. One week before admission the patient developed a nasal discharge which was followed within a few hours by a sharp, continuous pain about the right eye and, four days later, by swelling of the right eye and diplopia on looking to the right. There were no chills, nausea or vomiting.

Examination.—Temperature 100° F.; pulse 90; respiration 20; blood-pressure 125/80.

The sensorium was clear. The neck was stiff. There was slight proptosis, chemosis, "slight papillœdema," and complete ophthalmoplegia of the right eye. Vision was not impaired, and the visual fields were normal. Tests of motor and sensory function disclosed nothing remarkable.

Laboratory data.—White blood cells 14,000, 88 per cent. polymorphonuclear leucocytes. Cerebrospinal fluid (on sixth hospital day): Pressure 350 mm.; cell count 15 per c.mm., all lymphocytes; total protein 71 mgm. per cent. and sugar 77 mgm. per cent.; Lange reaction 0011222100. X-ray: "Clouding of the left frontal and ethmoid sinuses."

Course.—The proptosis and ophthalmoplegia on the right diminished a little during the first three hospital days. The left eye then became swollen. On the sixth hospital day the patient was drowsy and had a headache and high fever. There was papillœdema bilaterally and a left facial weakness. On the tenth hospital day there was a generalized convulsion, followed by a left hemiplegia and paralysis of conjugate movements of the eyes to the left. Death occurred on the nineteenth day of illness, six days after onset of generalized headaches and two days after the appearance of focal neurological signs.

Pathological findings.—Subdural empyema, right, with advanced organization next the dura. Acute suppurative sinusitis, right sphenoid and ethmoid. Thrombophlebitis of both cavernous sinuses and right middle cerebral vein. Orbital abscess, left. Localized acute meningitis. Necrosis of cerebral cortex.

Comment.—It seems likely that retrograde thrombophlebitis extending from the cavernous sinus along the middle cerebral or other tributary veins was responsible for the subdural infection. No evidence of direct extension was found, and the superior longitudinal sinus was normal. Aside from

the middle cerebral vein no other thrombosed meningeal veins were observed, and the cerebral cortex was not hæmorrhagic.

Case 7.—Male, aged 41. *History:* Five weeks before admission, after the extraction of an upper tooth abscess, the antrum on that side became infected and was treated with frequent irrigations. Symptoms of sinus infection continued and five days before admission the patient developed frontal and occipital headache. Three days later he became restless and irrational and ten hours before admission he became aphasic.

Examination.—Temperature 101° F.; respiration 25; blood-pressure 120/80.

Patient was stuporous and unable to speak but could understand at least part of what was said to him. His neck was stiff. Optic fundi and visual fields were normal. There was weakness of the right side of the face and of the right arm and leg. The tendon reflexes were more active on the right; abdominal reflexes were absent, and there was a Babinski sign on both sides. No sensory loss was demonstrated.

Laboratory data.—White blood cells 23,100, 90 per cent. polymorphonuclear leucocytes. Cerebrospinal fluid: Pressure 220 mm.; cells 146 per c.mm., 74 per cent. polymorphonuclear leucocytes; protein 166 mgm. per cent.; Lange reaction 00123331000. X-ray: "Chronic left pansinusitis. Displacement of pineal shadow to the right and posteriorly."

Course.—Two days after admission a left temporal craniotomy was performed. There was a moderate amount of subdural fluid and the cerebral cortex appeared congested. The next day the left frontal sinus was opened and found to contain thickened membrane and polypoid tissue; the posterior wall of the sinus was removed, disclosing a small area of epidural granulation tissue in which there was a small perforation discharging pus, and on incision of the dura a large amount of subdural pus was obtained. The patient improved slightly but then relapsed and died two days later, ten days after the onset of generalized headache and five days after the appearance of focal neurological signs.

Pathological findings.—Subdural empyema, left, extending beyond falx to right anterior frontal region. Chronic sinusitis, left frontal, with underlying epidural granulations and perforation of dura. Thrombophlebitis of subarachnoid veins. Localized acute meningitis. Necrosis and venous hæmorrhages of cerebral cortex and subcortical white matter.

Comment.—Although at autopsy an adherent thrombus in the superior longitudinal sinus was thought to have been observed, no thrombus could be seen in microscopic sections. Next the subdural exudate, however, there was necrosis and polymorphonuclear infiltration of the sinus wall. The process did not involve the intima and seemed to be extending from without inward. Epidural granulations and perforation of the dura, found at operation, indicate that there had been direct extension of the infection.

Case 8.—Female, aged 49. *History:* During the past year the patient had had several operations for removal of polyps and drainage of pus from the right frontal sinus, but pus continued to drain through a fistula above the right eye. Then she developed swelling of the orbital tissues and forehead on the right side and was sent to the hospital with a diagnosis of frontal osteomyelitis, which was confirmed

by X-ray examination. At operation when the diseased frontal bone was removed about 5 c.c. of epidural pus was found. The patient continued to have irregular fever ranging from 100° to 102·5° F. More necrotic bone was removed at two subsequent operations. Two days after the last operation, or on the seventeenth hospital day, the temperature rose to 104° F. No other abnormal findings were noted. The next day the patient was confused and stuporous; the neck was moderately stiff; there was weakness of the face on the left side, and paralysis of conjugate movement of the eyes to the left; the left knee-jerk was more active than the right and plantar reflexes were equivocal. The patient became more stuporous and had frequent left-sided and generalized convulsions. On the twenty-first hospital day she lapsed into coma and died, three days after the appearance of focal neurological signs. No mention of headache appears in the record.

FIG. 1.—View of superior surface of the brain with dura intact (brow up). Note: (1) Epidural granulation tissue in frontal regions. (2) Thick, white, opaque dura obscuring meningeal vessels of the right and the frontal part of left cerebral hemispheres.

Laboratory data.—Cerebrospinal fluid (seventeenth and twentieth days of illness): Pressure 250 and 385 mgm.; cells 90 per c.mm.. 76 per cent. polymorphonuclear leucocytes; protein 47 mgm. per cent.; sugar 74 mgm. per cent.; Lange reaction 1123210000. X-ray: "Osteomyelitis of frontal bone on right."

Pathological findings.—Subdural empyema, right, with organization. Pansinusitis, chronic and acute suppurative. Frontal osteomyelitis. Orbital abscess, right. Localized acute meningitis. Thrombophlebitis of subarachnoid and cerebral veins (organized thrombi). Degeneration and hæmorrhages of cerebral cortex and subcortical white matter. Subpial abscess (0·5 cm.).

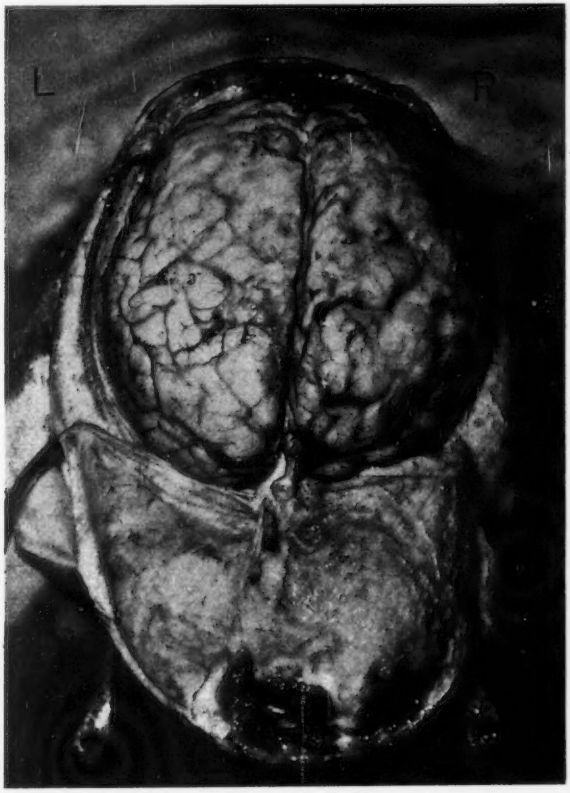

FIG. 2.—View corresponding to fig. 1 but with the dura reflected backwards. Purulent exudate covers the arachnoid of right and frontal part of the left cerebral hemispheres.

Comment.—There was organization of the subdural exudate next the dura. Organized and recent, septic and bland thrombi were observed in the subarachnoid veins. The superior longitudinal sinus was normal and infection undoubtedly was the result of direct extension.

by X-ray examination. At operation when the diseased frontal bone was removed about 5 c.c. of epidural pus was found. The patient continued to have irregular fever ranging from 100° to 102·5° F. More necrotic bone was removed at two subsequent operations. Two days after the last operation, or on the seventeenth hospital day, the temperature rose to 104° F. No other abnormal findings were noted. The next day the patient was confused and stuporous; the neck was moderately stiff; there was weakness of the face on the left side, and paralysis of conjugate movement of the eyes to the left; the left knee-jerk was more active than the right and plantar reflexes were equivocal. The patient became more stuporous and had frequent left-sided and generalized convulsions. On the twenty-first hospital day she lapsed into coma and died, three days after the appearance of focal neurological signs. No mention of headache appears in the record.

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Laboratory data.—Cerebrospinal fluid (seventeenth and twentieth days of illness): Pressure 250 and 385 mgm.; cells 90 per c.mm.. 76 per cent. polymorphonuclear leucocytes; protein 47 mgm. per cent.; sugar 74 mgm. per cent.; Lange reaction 1123210000. X-ray: "Osteomyelitis of frontal bone on right."

Pathological findings.—Subdural empyema, right, with organization. Pansinusitis, chronic and acute suppurative. Frontal osteomyelitis. Orbital abscess, right. Localized acute meningitis. Thrombophlebitis of subarachnoid and cerebral veins (organized thrombi). Degeneration and hæmorrhages of cerebral cortex and subcortical white matter. Subpial abscess (0·5 cm.).

FIG. 2.—View corresponding to fig. 1 but with the dura reflected backwards. Purulent exudate covers the arachnoid of right and frontal part of the left cerebral hemispheres.

Comment.—There was organization of the subdural exudate next the dura. Organized and recent, septic and bland thrombi were observed in the subarachnoid veins. The superior longitudinal sinus was normal and infection undoubtedly was the result of direct extension.

FIG. 3.—Subdural exudate covering the arachnoid and moulding the right cerebral hemisphere.

In this case, so far as one can judge from the recorded clinical data, the patient did not seem to be seriously ill until four days before death; yet organization of the exudate indicates the subdural infection antedated the onset of alarming symptoms. Organization of thrombi in the meningeal veins points in the same direction.

Case 9.—Male, aged 54. *History :* The patient entered the hospital because of supra-orbital pain and nasal discharge of three months' duration. On admission there was swelling and tenderness over the right frontal sinus and roentgen examination at this time revealed osteomyelitis of the frontal bone. Sulfapyridine was administered and several operations for removal of necrotic frontal bone were performed. A small collection of epidural pus was found. There was low grade irregular fever from the time of entry. On the thirty-ninth hospital day the temperature rapidly rose to 103° F. and the patient became confused.

Neurological examination.—When seen at this time the patient was stuporous and his neck was quite stiff. There was slight papilloedema. Tendon reflexes were slightly less active on the right and plantar reflexes were extensor on both sides.

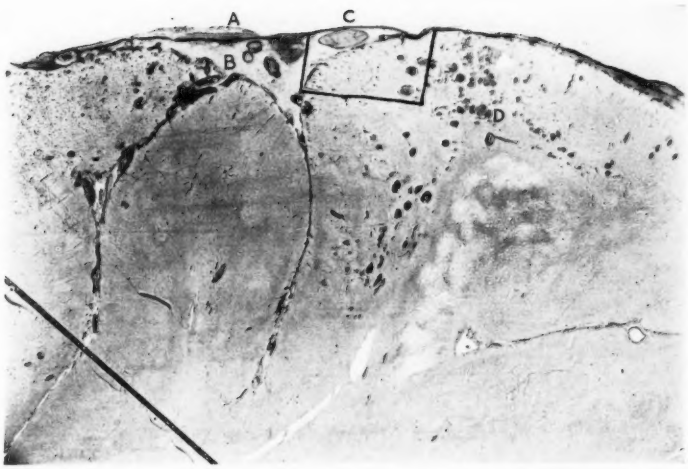

FIG. 4.—Low power view showing: A, small amount of subdural exudate on outer surface of arachnoid membrane; B, subarachnoid exudate; C, subarachnoid vein containing septic thrombus; D, small cortical hæmorrhages.

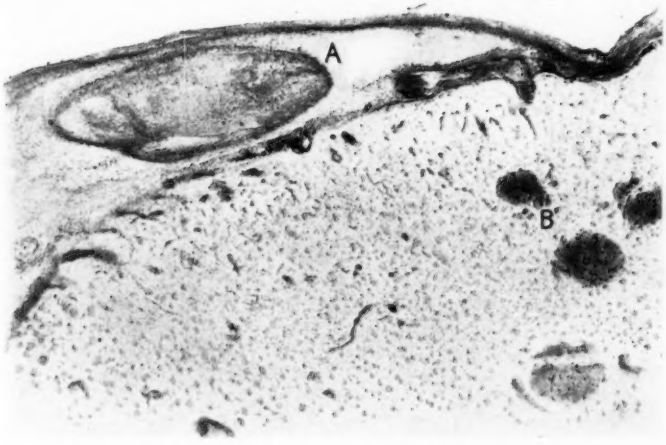

FIG. 5.—High power view of area outlined in fig. 4: A, Thrombosed meningeal vein; B, cortical hæmorrhages.

To illustrate article by Charles S. Kubik and Raymond D. Adams.

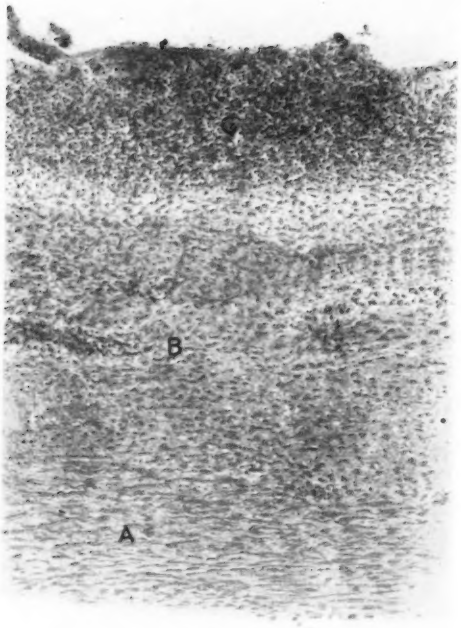

FIG. 6.—A, dura; B, perivascular infiltration with lymphocytes and polymorphonuclear leucocytes; C, subdural exudate. There is no organization of the subdural exudate.

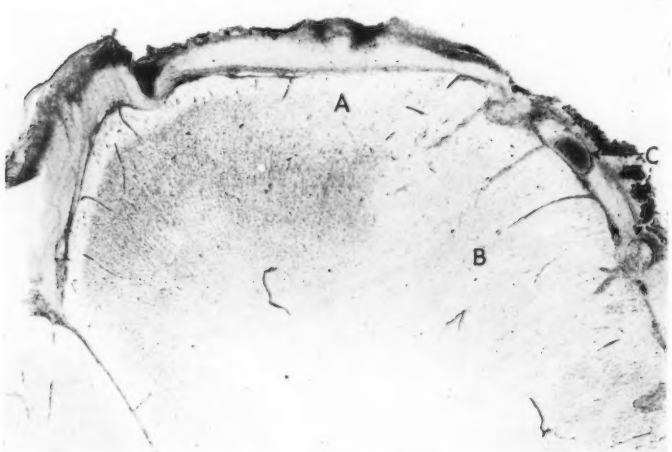

FIG. 7.—Necrosis involving A in predominantly the outer zone of grey matter and B both grey and white matter; C, thrombosed subarachnoid veins.

To illustrate article by Charles S. Kubik and Raymond D. Adams.

Laboratory data.—White blood cells 31,100, 84 per cent. polymorphonuclear leucocytes. Cerebrospinal fluid: Pressure 200-230 mm.; cells 166 per c.mm., 56 per cent. polymorphonuclear leucocytes; protein 104 mgm. per cent.

Course.—Stupor increased and on the forty-second hospital day the patient was comatose and had a right hemiplegia. A burr hole was made in the left frontal region and 80 c.c. of pus from the subdural space was obtained. After operation there were many right-sided convulsions. Drainage of the subdural exudate was inadequate, and on the forty-fifth hospital day a left temporal craniotomy was performed and 50 c.c. of pus removed. The convulsions continued, the pulse fell from 110 to 60, and death occurred on the forty-eight hospital day, or nine days after the onset of focal neurological signs. Cerebrospinal fluid shortly before death contained 2,300 cells per c.mm., 95 per cent. of which were leucocytes; sugar content was 56 mgm. per cent.

Pathological findings.—Subdural empyema, left, with extension to right frontal region. Organization on right, not on left. Acute suppurative sinusitis, left frontal and sphenoid. Osteomyelitis of frontal bone. Epidural granulations. Localized subacute meningitis. Thrombosis of subarachnoid veins. Necrosis and numerous small hæmorrhages of cerebral cortex.

Comment.—There was organization in the external layer of the subdural exudate on the left side but no organization on the right. Many of the subarachnoid veins were occluded or partially filled by recent and organized bland thrombi; some were occluded by recent thrombi on mural, organized thrombi. One medium-sized vein in the cerebral cortex contained an organized bland thrombus. The subarachnoid exudate was scanty and largely lymphocytic. The findings indicate a long-standing and relatively benign infection which might conceivably have responded to adequate drainage instituted earlier in the course of the disease. The probable pathway of infection was by direct extension from the frontal sinus.

Case 10.—Male, aged 22. *History:* Two weeks before entry to the hospital this patient developed severe pain in the middle of the forehead and slight nasal discharge. The headache persisted and, the next day, was associated with fever, nausea, vomiting and insomnia. Four days later the left upper eyelid became red and swollen. On the sixth day of illness a pocket of pus was drained through an incision below the left eyebrow. The vomiting and frontal headache diminished during the next few days, but on the tenth or eleventh day the patient became delirious and headache returned with increased severity. On the twelfth day he became irrational and at times uncommunicative and was taken to a local hospital. The next day he had a right hemiplegia. Soon afterwards he became comatose and the following day was transferred to the Massachusetts General Hospital. Before the present illness the patient was known to have had a deviated nasal septum but no definite history of sinusitis.

Examination.—Temperature 102 to 105° F.; pulse 76; respiration 20; blood-pressure 130/60.

On entry the patient was comatose. Other findings were: Œdema of left upper eyelid; a draining sinus beneath the left eyebrow; slight venous engorgement in optic fundi; weakness of left external rectus: flaccid right hemiplegia; increased tendon

reflexes on the right side, absent abdominal reflexes and bilateral extensor plantar responses. On the following day right-sided convulsive seizures supervened.

Laboratory data.—White blood cells 33,800, 90 per cent. polymorphonuclear leucocytes. Cerebrospinal fluid: Pressure 275 mm.; cells 450 per c.mm., 88 per cent. polymorphonuclear leucocytes; protein 164 mgm. per cent.; sugar 56 mgm. per cent.; chlorides 811 mgm. per cent.; Lange reaction 1234442100. X-ray: "No evidence of osteomyelitis. Left frontal and ethmoid slightly more opaque than right." Electro-encephalogram: "5 to 6 per second waves and some 18 per second waves from all 16 leads. Over the left side in the fronto-parietal region the voltage was depressed."

Course.—Operation disclosed frontal osteomyelitis; pus in the left frontal sinus; epidural granulations; and a left frontal lobe abscess, which was drained. Heparin and sulfathiazol were given. The patient continued to have right-sided convulsions and died twenty-two hours after the operation on the fifteenth day of illness and two days after the onset of focal neurological signs.

Pathological findings.—Subdural empyema, left (with organization). Cerebral abscess, left frontal. Acute suppurative sinusitis, left frontal. Orbital abscess, left. Localized acute meningitis. Thrombosis, with organization of subarachnoid veins. Necrosis and hæmorrhages of cerebral cortex and subcortical white matter. Temporal pressure cone, left.

Comment.—Necrosis of cortex and white matter was very extensive and unusually hæmorrhagic. It was in a large hæmorrhagic softening of the white matter that the cerebral abscess was situated. Although there was organization of the subdural exudate, there was not the slightest encapsulation of the cerebral abscess, which apparently was a much more recent process, and probably developed as a result of infection spreading along thrombosed veins to devitalized tissues. It is of interest that the subdural empyema was not detected when the cerebral abscess was drained through the frontal sinus.

Case 11.—Male, aged 12. *History:* The patient was a moron in a State hospital and was known to have had chronic otitis media for years. One month before admission he had a fever, pain in the right ear and vomiting, but these symptoms lasted only one day. He remained well then until four days before admission, when he again vomited and complained of severe right-sided headache. These symptoms continued until the time of admission.

Examination.—Temperature 105° F.; pulse 120; respiration 30.

The mental status varied from a condition of stupor to one of restlessness and irritability. The neck was stiff and a Kernig sign was present. The optic fundi were normal; visual fields could not be accurately tested. There was a left hemiparesis. All the extremities were withdrawn from painful stimuli. The tendon reflexes were about equal on the two sides, but the left abdominal reflex was diminished and plantar reflex was extensor on the left, flexor on the right.

Laboratory data.—White blood cells 30,700, 92 per cent. polymorphonuclear leucocytes. Cerebrospinal fluid: Pressure 70 mm.; cells 840 per c.mm., 40 per cent. polymorphonuclear leucocytes.

Course.—The next day the patient was comatose and had a left hemiplegia.

A radical mastoidectomy was performed on the second hospital day; the tegmen was necrotic and the dura was reported to be normal. The patient died on the third hospital day or on the seventh day of his illness and three days after the appearance of focal neurological signs.

Pathological findings.—Subdural empyema, right. Acute suppurative otitis media, mastoiditis and petrositis; necrosis of tegmen, with a small epidural collection of pus and perforation of overlying dura. Localized acute meningitis. Thrombosis of subarachnoid veins. Necrosis of cerebral cortex.

Comment.—All of the venous sinuses were normal, infection having extended through the tegmen and perforated dura. The subdural exudate, as in the other cases, was most abundant in the lower lateral frontal region.

Case 12.—Male, aged 24. *History:* One year ago he lost weight and had a chronic cough, purulent sputum and hæmoptysis, which led to a diagnosis of pulmonary tuberculosis. Eight days before admission he had influenza and a pain in the left ear, but he continued to work. On the fifth day of the illness he had severe headache and weakness of the right arm, followed shortly by hemiplegia. On the seventh day he was unable to speak and the next morning could not be aroused.

Examination.—Temperature 102° F.; pulse 52; respiration 25; blood-pressure 140/50.

His neck was stiff. The right pupil was larger than the left, which did not respond to light. There was a right hemiplegia. Tendon reflexes were increased on the left, abdominal reflexes were absent and both plantar reflexes were extensor. There was clubbing of the fingers and cyanosis of the lips and nail beds.

Laboratory data.—Cerebrospinal fluid: Pressure 350 mm.; cells 210 per c.mm., mostly lymphocytes; protein 120 mgm. per cent.; sugar normal.

Course.—On the day of admission a burr hole was made in the left mid-parietal region. When the dura was incised, 100 c.c. of thick yellow pus escaped. The patient soon began to have right-sided convulsive seizures and died fifteen hours after operation on the eighth day of illness and three days after the onset of focal neurological signs.

Pathological findings.—Subdural empyema, left. Multiple metastatic cerebral abscesses. Localized acute meningitis. Bronchiectasis and bronchiectatic abscesses.

Comment.—Among the cerebral abscesses, none of which measured over 1·5 cm. in diameter, were several immediately beneath the pia and it may be that infection extended to the subdural space from one of these, though to do so it would have to cross the subarachnoid space and pass through the arachnoid membrane. The subarachnoid veins were not thrombosed and neither necrosis nor hæmorrhages of the cerebral cortex were observed. (Microscopic sections of the entire hemisphere were not made.) There was beginning organization of the subdural exudate, which, as in the other cases, was most abundant in the lower lateral frontal region.

Case 13.—Male, aged 14. *History:* The patient became ill three weeks before entry to the hospital. During the first few days fever and malaise were the only symptoms and the diagnosis was thought to be influenza. About two weeks before admission there was nasal discharge and discomfort around the eyes, and, one week

later, severe generalized headache and vomiting. A few hours before coming to the hospital the patient became drowsy and developed weakness of his left arm.

Examination.—Temperature 104° F.; pulse 120; respiration 20; blood-pressure 120/78.

The patient was stuporous and his neck was stiff. There was slight swelling around the right eye and tenderness over the right frontal sinus. The margins of the optic disc were blurred. Visual fields could not be tested. There was limitation of left lateral conjugate movement of the eyes. Pupillary reflexes were normal. There was left hemiparesis affecting the face, arm and leg.

Laboratory data.—White blood cells 19,000, 84 per cent. polymorphonuclear leucocytes. Cerebrospinal fluid: Pressure 300 mm.; cells 26 lymphocytes per c.mm.; protein 126 mgm. per cent.; sugar normal. X-ray: "Clouding of right frontal and ethmoid sinuses."

Course.—Within a few hours the patient became comatose. On the second hospital day a right temporal craniotomy was performed. When the dura was incised a large quantity of greenish-yellow pus escaped. There was immediate improvement, but convalescence was slow. The function of the left arm gradually returned and when last heard from the patient was entirely well.

Case 14.—Male, aged 15. *History:* For the previous four or five months this patient had had frequent colds with considerable nasal discharge and post-nasal drip. Two days before entry he again developed symptoms of a cold and severe right frontal headache. The next day the right eye was swollen and temperature was 102° F. The headache persisted and his condition was unchanged when he was admitted to the hospital on the third day of his illness. Except for orbital swelling and tenderness over the frontal sinus on the right side physical examination was negative. Temperature was 99·4° F. On the third hospital day the temperature rose to 103° F. and the patient had a series of convulsive seizures, which began on the right side. When examined at this time he was stuporous, there was hemiparesis with extensor plantar response on the right side, and the neck was rigid. The seizures increased in frequency until they occurred about every five minutes. The patient was taken to the operating room to be explored for subdural abscess but because of severe respiratory difficulty operation was deferred. The seizures were finally controlled by ether anæsthesia. Sulfapyridine and heparin were administered. The patient regained consciousness but had right hemiplegia and aphasia Two days later headache increased and the patient became less responsive. On the sixth hospital day, three days after onset of seizures and hemiparesis, a left-sided subdural empyema was drained through a lateral frontal craniotomy. Convalescence was stormy. There were numerous convulsive seizures. Paralysis of conjugate deviation of the eyes to the right was present for a time. Several days after the operation power in the paralysed arm and leg began to return, speech was regained, the convulsions ceased, and there was a slow, steady improvement. When discharged, seven and a half weeks after the operation, the only abnormal findings were slightly increased tendon reflexes on the right side.

Laboratory data (before operation).—White blood cells 27,000. Cerebrospinal fluid: Pressure 230 mm.; cells 21 per c.mm., 57 per cent. polymorphonuclear leucocytes; protein 58 mgm. per cent.; sugar 103 mgm. per cent.: chlorides 690 mgm. per cent. Blood cultures were repeatedly negative. *Staphylococcus aureus* was grown from the subdural exudate.

No conclusive clinical or X-ray evidence of frontal or ethmoid sinusitis was demonstrated before operation. Three weeks later there was cloudiness of the left

frontal sinus, but no signs of osteomyelitis. Two weeks after discharge, however, X-ray examination revealed frontal osteomyelitis, which was successfully treated by removal of the diseased bone. Old thrombophlebitis of the superior longitudinal sinus was observed at the operation.

Final note.—The patient has had several convulsive seizures and is taking dilantin. Mental and neurological status in other respects is normal.

Discussion.

Contrary to prevailing opinion, subdural empyema is not an uncommon form of intracranial infection. Hecquet (1934) collected more than 40 cases between 1924 and 1933. Courville and Nielsen (1934) found 32 cases in 10,000 autopsies, among which there were 54 brain abscesses and 817 cases of meningitis, all complicating otitis and sinusitis. Mygind (1921) found 19 in 207 cases of intracranial complications of otitis media. In a four-year period, among approximately 1,600 autopsies at the Massachusetts General Hospital and Massachusetts Eye and Ear Infirmary, there were 11 cases, 10 complicating sinusitis and one of otitic origin, together with 27 brain abscesses and 41 cases of meningitis, all secondary to infections of ears or paranasal sinuses.

It is probably no coincidence that 13 of our 14 cases occurred in males. This has been noted by other writers on the subject, but no plausible explanation has been advanced. Eight of our 14 cases were between the ages of 12 and 30 years, the others ranging between 30 and 55 years.

The factors which lead to subdural empyema rather than cerebral abscess or leptomeningitis, are not understood. It has been said that a chronic ear or sinus infection favours the formation of subdural empyema because there is time for limiting meningeal adhesions to form, thus preventing the rapid dissemination of bacteria to the meninges, but it has been our experience that brain abscess and meningitis also usually follow chronic infections. In the majority of our cases there had been chronic infections with acute exacerbation shortly before the onset of the subdural infection. In one (Case 6), however, there was an acute sinusitis without any history of previous sinus infection, while in another (Case 5) the condition followed operative fracture through the posterior wall of the frontal sinus, apparently in the absence of suppurative sinusitis.

It would seem that chronic frontal sinusitis with frontal osteomyelitis and epidural infection is particularly favourable to the development of subdural empyema. The type of organism may possibly be a determining factor. An adequate bacteriological study unfortunately was not made in this group of cases.

Symptomatology.

In a majority of the cases there was an acute exacerbation of chronic sinusitis (or otitis). Local pain was referred to the region of the involved sinus or ear. In the sinus cases it was usually located over the brow or between the eyes. Tenderness and pain on pressure over the affected sinus was usually present. Orbital swelling was present in all the sinus cases and in all but one case (Case 14) was on the side of the subdural empyema.

Elevation of temperature, general malaise, and irritability were early symptoms. Two of the patients experienced hard shaking chills. The temperature generally rose to 102 to 105° F.

Severe headache, the earliest and most persistent symptom, was present in every case where accurate history was available. In the beginning pain was localized to the region of the involved sinus. Later there was severe, generalized headache. Vomiting was frequent, with or without antecedent nausea.

Stiffness of the neck was present in every case even when the spinal fluid contained a relatively small number of cells. The Kernig sign was sometimes, though usually not, present.

Sooner or later a change in the patient's state of consciousness occurred, beginning with confusion, inattention or somnolence and progressing to stupor and coma.

In a majority of the patients with left-sided lesions there was an aphasia which consisted of inability to speak but retention of the ability to comprehend spoken language. In some it was the earliest focal sign.

A very frequent sign was paralysis of conjugate movement of the eyes to the contralateral side. Occasionally the eyes even deviated towards the side of the lesion. In one such case (Case 14), however, deviation toward the contralateral side would still occur during a Jacksonian seizure.

Contralateral hemiparesis or hemiplegia developed in all of the cases. The tendon reflexes on the affected side were decreased in some instances and increased in others; the abdominal reflex was usually diminished or absent and the plantar response extensor in type. In the terminal stages an extensor plantar response was often obtained on both sides.

Convulsions were present in seven of the fourteen cases. These always began as Jacksonian seizures on the contralateral side, in one case before and in others after the onset of paralysis. Beginning as a Jacksonian seizure, the convulsion often became generalized. In some instances convulsions occurred with such frequency as to be almost continuous.

Sensory changes of the cortical type were not observed in any case.

Stupor, delirium, or aphasia usually precluded accurate sensory examination. No visual field defects were found, though here again poor co-operation may have prevented their detection.

In the late stages, as intracranial pressure continued to rise, the pulse often became full and slow and the blood-pressure rose. The respiratory rhythm became Cheyne-Stokes in type. After lumbar puncture and reduction of spinal fluid pressure the pulse would often become rapid and blood-pressure was reduced for a few hours. Papilloedema was recorded only once (Case 6); in this instance it was slight and may have been due to thrombophlebitis of the cavernous sinuses.

Taking the symptoms in the order of their appearance, the following sequence of events was generally noted: There was an antecedent sinusitis or otitis and, in the cases complicating sinusitis, orbital swelling. At the start there was pain or headache usually localized to the frontal region on the side of the subdural infection. Then the headache became more severe and generalized. There was a marked rise in the temperature and the patient appeared to be seriously ill. The neck was rigid. After a variable interval of time, usually not exceeding a few days, drowsiness and increasing stupor, rapidly progressing to coma, supervened. At about the same time focal neurological signs began to appear, the most important ones being Jacksonian seizures, hemiparesis or hemiplegia, aphasia and paralysis of lateral conjugate movement of the eyes. With the appearance of focal signs the course was rapidly downhill and death in the fatal cases occurred from two to five days later.

Laboratory data.—In the majority of the cases X-ray examination revealed some evidence of frontal or ethmoid sinusitis. In one (Case 5) the findings were questionable. In another (Case 14) there was no X-ray evidence of sinusitis before operation, though there had been symptoms of it; frontal osteomyelitis, recognized by X-ray, developed later. In two (Cases 8 and 9) frontal osteomyelitis was detected at the first examination.

Cerebrospinal fluid.—As may be seen in Table I, p. 41, the significant findings generally were increased pressure; pleocytosis of a moderate degree, polymorphonuclear leucocytes predominating; elevated protein content; normal sugar content. Bacteria was never demonstrated in smears or by culture.

The white blood cells were always increased, ranging from 15,000 to 35,000 per c.mm. and there was a polymorphonuclear leucocytosis.

In only one of our cases was an electro-encephalogram obtained. In addition to large delta waves over the entire cortex (the patient was semi-

comatose at the time), there was lowered voltage in the leads situated over the thickest portion of the subdural abscess. Jasper (1940) has reported a similar lowering of voltage over subdural hematoma. It is supposed that the thick layer of blood (or pus, as in this case) interposed between cerebral cortex and electrode interferes with the transmission of brain waves. Similar findings would have to be obtained in other cases before one could attach much significance to such an observation.

Diagnosis.—The first essential in the diagnosis of subdural empyema is the recognition of intracranial infection. All too often the earlier symptoms, such as headache, vomiting and drowsiness, are not given the attention which they deserve and are attributed to sinusitis, mastoiditis or osteomyelitis.

In the earlier stages, particularly before the appearance of focal neurological signs, the possibility of meningitis may be suggested by the rigidity of the neck, but can be ruled out by examination of the spinal fluid. As a matter of fact, rigidity of the neck with elevated pressure, only slight or moderate pleocytosis, absence of organisms, and with normal sugar and chlorides is strongly suggestive of subdural empyema.

Epidural abscess, in our experience, does not resemble subdural empyema in its clinical manifestations. The patient is not so ill; there is seldom rigidity of the neck; and focal signs rarely, if ever, occur. Actually, the finding of epidural suppuration at operation for frontal sinusitis or osteomyelitis is an additional reason for suspecting subdural empyema if there are other symptoms pointing in that direction.

Once focal neurological signs have developed only thrombosis of the superior longitudinal sinus and cerebral abscess need be seriously considered. The clinical resemblance between subdural empyema and thrombosis of the superior longitudinal sinus is close and reference has already been made to their possible co-existence. Favouring the diagnosis of sinus thrombosis are: a septic temperature. absence of increased intracranial pressure or of stiff neck, little or no pleocytosis and the occurrence of bilateral signs such as focal convulsions or paralysis first on one side of the body, then on the other.

Cerebral abscess can be distinguished from subdural empyema in most cases. The initial stage is milder and more insidious in onset and the course is usually more protracted. Some remission of the headache may occur. The temperature is seldom high and may be normal. Rigidity of the neck rarely occurs except in the case of a complicating meningitis. When cells are present in the spinal fluid, the number, as a rule, is small and lympho-

cytes predominate. In a group of fifty cerebral abscesses, now being studied, an occasional case had high intracranial pressure and a short, fatal course. This form of "acute cerebral abscess" might possibly be confused with subdural empyema. In case of doubt burr-hole exploration for subdural empyema would be in order.

Gross pathology.—Except for the source and the pathway of infection the pathological findings were remarkably similar in each case. In the cases complicating sinusitis, infection of the subdural space took place by direct extension in 7, as a result of thrombophlebitis of the superior longitudinal sinus in 2, while in 1 it was not clear which was responsible. In 4 of the 7 cases extension through the dura followed osteomyelitis of the frontal bone; in 2 it followed necrosis or perforation of the bony wall of the frontal sinus or ethmoid cells and dura; and in 1 it followed an operative fracture.

The subdural exudate generally covered a large part of one cerebral hemisphere. The pus was most abundant in the lower lateral frontal region, anterior to the motor cortex and as a rule extended to the medial and orbital surfaces, to the temporal lobe and as far back as the parietal or posterior parietal region. In some cases it extended beneath the falx to the opposite hemisphere. It was never walled off. In older cases, there was organization of the exudate in a thin layer on the inner surface of the dura, but never a limiting membrane surrounding the exudate or separating it from the arachnoid membrane. Beneath the subdural exudate the lateral surface of the frontal lobe was always depressed, as in subdural hæmatoma.

Limited more or less to the area covered by the subdural exudate there was regularly a purulent subarachnoid exudate. It was unusual to find any visible subarachnoid exudate on the base of the brain or brain-stem. Thrombosis or thrombophlebitis of subarachnoid veins could usually be demonstrated and in many cases the surface of the brain and cut surfaces of the cortex and subcortical white matter were hæmorrhagic.

Microscopic findings.—On the inner surface of the dura there was a layer of fibrinous, polymorphonuclear exudate. which, in some of the older cases, was organized next the dura. Within the dura itself, particularly in the inner layer, there was often infiltration with polymorphonuclear leucocytes or leucocytes and lymphocytes, occasionally thrombophlebitis and rarely miliary abscesses. In one case (Case 3), where infection by direct extension was demonstrated and the superior longitudinal sinus did not seem to be thrombosed at autopsy, microscopic examination revealed septic

mural thrombi, apparently secondary to the subdural infection, attached to infiltrated and necrotic portions of the sinus wall. Beneath the subdural exudate a polymorphonuclear subarachnoid exudate was regularly found. A pronounced basilar meningitis was not observed.

Thrombosis of subarachnoid veins was observed in all but one case (Case 5). In some only a few vessels were involved in the material examined; in others nearly every vein was affected. A large proportion of the thrombi were free of cellular infiltration and did not appear to be "septic." Some were purulent. In a number of older cases organized thrombi were found. Mural thrombi, only partly filling a vein, were a common finding. These formed where the vessel wall was necrotic, usually on the side of the vein nearest the subdural exudate, from which it was separated by arachnoid which appeared to be necrotic. Some of these mural thrombi were partly organized and in some instances there was an old mural thrombus with superimposed recent thrombosis obliterating the vessel. Venous thrombi within the substance of the brain were found occasionally.

Necrosis, more or less severe, of the underlying cerebral cortex and subcortical white matter was observed in every case. It was most pronounced in the outer layers of the grey matter, but usually there were regions where it extended for a considerable distance into the white matter. The histological changes were practically identical with those of recent infarction resulting from arterial occlusion, but the affected tissues were as a rule considerably more hæmorrhagic. In a majority of the cases the changes were quite recent and consisted of shrunken "ischæmic" nerve cells, pyknotic glia nuclei, and slight to moderate polymorphonuclear infiltration. In one case there was intimal and adventitial proliferation and scattered microglial phagocytes, indicating that the process had occurred at least several days before death.

In the otitic and metastatic cases both gross and microscopic findings were similar to those described above except for the pathway by which infection reached the subdural space. In the first there was direct extension from the middle ear through the tegmen and dura. In the latter the source of the infection seemed to be a small, metastatic, subpial abscess.

The findings indicate that the infection reaches the subdural space by direct extension in most cases and as a result of thrombophlebitis in others. The subdural exudate is not walled off and probably continues to spread up to the time of death. Thrombosis of subarachnoid and cerebral veins is, we believe, secondary to the subdural or subdural and arachnoid infections, since it is observed not only when the infection results from sinus

thrombosis, but also when it takes place by direct extension. Further indication that this is so is provided by necrosis of vessel walls and mural thrombi on the side of vein nearest the subdural infection. Thrombosis beginning in the subarachnoid veins extends, in some cases, to the small tributary branches within the brain. Degenerative changes in the brain occur, however, when only the subarachnoid veins are thrombosed. We believe that venous infarction is largely responsible for the severe symptoms, particularly the focal signs, observed in the later stages of the illness. The rapid progression of these symptoms would tend to support this view. It may very well be that compression of the brain by the empyema is also a factor. The hæmorrhages, it seems likely, are of minor importance; they probably occur after the damage has been done, and in some cases are not even present in areas of severe necrosis.

Treatment.—Subdural empyema is a fulminating disease, rapidly terminating in death if untreated. Too often the condition is not recognized or even suspected, or operation is delayed until some time after the onset of coma and hemiplegia, when any treatment is likely to be ineffective. Early diagnosis and operation would unquestionably result in a lower mortality. It is true that one may not be very certain of the diagnosis before the onset of focal signs, but the early symptoms should lead one to suspect the condition or at least to keep it in mind, so that exploration may be undertaken when focal signs first appear. Both of the successfully treated patients in our series had focal signs before they were operated on.

We believe that the operation of choice is drainage through an enlarged burr-hole in the lateral, frontal region, where the largest accumulation of pus has invariably been found. Aside from the fact that more pus is evacuated and better drainage results, several other considerations favour this approach. It is a clean field; exposure is easy; a good view is obtained of the dura; and the findings are not obscured by granulations, thickening of the dura, or changes resulting from previous operations. The dura over a subdural abscess looks white, because of the pus underneath, in striking contrast to the normal appearance. By simply exposing the dura one can usually, if not always, tell whether subdural exudate is present or not, although in case of doubt there should be no serious objection to incision of the dura in a clean field, so long as the exploration does not include probing of the brain.

We believe that when the diagnosis of subdural empyema is reasonably certain, or even a likely possibility, exploration should not be delayed. The situation should be regarded as an emergency. Valuable time is often

lost operating on the sinuses or frontal osteomyelitis. Once the infection has entered the subdural space, these are of secondary importance and can wait until after the intracranial condition has been relieved.

The sulfonamide drugs should obviously be used in accordance with generally accepted principles.

Summary.

The clinical features and pathological and surgical observations in fourteen cases of subdural empyema are described. The sources of infection were paranasal sinusitis in twelve cases, otitis media in one case, and bronchiectasis with metastatic infection in one case. The symptoms in the cases complicating sinusitis conformed to a fairly definite pattern, consisting of: exacerbation of chronic sinusitis; orbital swelling; headache, at first localized, later becoming generalized and increasing in severity; rise in temperature, as a rule to 103° F. or higher: stiffness of the neck: drowsiness or stupor; and focal neurological signs. Hemiparesis or hemiplegia occurred in every case. Paralysis of contralateral deviation of the eyes nearly always developed. Aphasia was observed in most cases of left-sided empyema. Jacksonian seizures were fairly common.

Spinal fluid pressure was nearly always increased, ranging from normal to the equivalent of 350 mm. of water. Cell counts generally ranged from 150 to 600 per c.mm., with polymorphonuclear leucocytes predominating. The sugar content of the spinal fluid was normal. The total protein ranged from 49 to 186 mgm. per 100 c.c. No organisms were found in smears or cultures.

Except for absence of sinus infection and orbital swelling, the clinical manifestations in the two other cases, secondary to otitis and to bronchiectasis, were similar to those complicating sinusitis.

The course was rapidly progressive. In twelve cases death occurred six to twenty days after onset of headache, and two to five days after focal signs were first observed. In two cases recovery took place after drainage of the empyema.

Infection of the subdural space took place by direct extension through the dura in a majority of the cases, and in the remainder, as a result of thrombophlebitis involving the venous sinuses, usually the superior longitudinal. The subdural pus in all cases covered the greater part of the lateral surface of the hemisphere, the greatest amount being situated over the lateral surface of the frontal lobe. There was regularly a localized subarachnoid exudate, conforming in its distribution to that of the sub-

dural exudate, but scarcely any generalized leptomeningitis. In the underlying cortical grey matter there was severe ischæmic necrosis and, in most cases, thrombosis or thrombophlebitis involving the subarachnoid veins.

Surgical treatment should consist of drainage through a lateral frontal craniotomy and not through the frontal sinus or a mastoidectomy wound. Performed in this way, the operation is simple and quick and, if the results are negative, little or no harm is done, provided that the brain is not explored.

TABLE I.—Summary of Clinical Data.

	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Sinusitis :														
Acute	+					+	+			+	—	—	+	+
Chronic	+	+	+	+	?	0	+	+	+		—	—		+
Orbital swelling	+	+	+	+	+	+	0	+	+	+	0	0	?	+
Fever	105	102	104	104	106	100	101	104	103	102	105	102	102	103
Chills	0	0	+	+	+	0	0	0	0	0	0	0	0	0
Headache	+	?	+	+	+	+	+	?	?	+	+	+	+	+
Vomiting	+	?	?	?	?	0	0	0	0	0	+	+	0	+
Stiff neck	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stupor-coma	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemiplegia	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Conjugate ocular paralysis	+	?	+	+	?	+	0	+	0	0	0	0	+	+
Convulsions	0	+	0	0	0	+	0	+	+	+	0*r*	+	0*r*	+
Aphasia	+	0*r*	+	?	0*r*	0*r*	+	0*r*	?	0	0	0	0	+
Cerebrospinal fluid :														
Pressure	165	160	310	350	280	350	200	250	230	275	70	350	300	230
Cells : Total per cent. pmn.	40	140	427	75	360	15	146	90	166	450	840	210	26	21
Per cent. pmn.	8	80	90	20	87	0	74	76	56	88	40	—	0	57
Protein	108	118	186	108	102	71	166	47	104	164	?	120	126	58
Sugar	93	?	?	113	89	77	?	74	56	56	?	nor.	nor.	103
Chloride	655	?	?	661	?	?	?		?	811	?	?	?	690
Duration in days from :														
Onset of headache	5	?	9–10	12	10	6	10	?	?	15	7	8	—	—
Onset of focal signs	1–12	2½	2	6	3–5	2	5	3	9	2	3	3	—	—
Result	D.	D.	D.	D.	D.	D.	D.	D.	D.	D.	D.	D.	R.	R.

r = Right-sided lesion. D. = Died. R. = Recovered.

TABLE II.—Summary of Pathological Findings.

	I	II	III	IV	V*	VI	VII	VIII	IX	X	XI†	XII‡
Sinusitis :												
Frontal	+	+	+	+	+	0	+	+	+	+	—	—
Ethmoid			+	+		+	0	+			—	—
Frontal osteomyelitis	0	+	0	0	0	0	0	+	+	+	—	0
Necrosis of bone			+	+			+?				+	
Epidural granulations	0	+	0	0	0	0	+	+	+	+	+	0
Sinus thrombophlebitis	+	0	+	+	0	Cav. sin. +	0	0	0	0	0	0
Organization of subdural exudate	0	+	0	0	+	+	+	+	+	+	0	+
Localized leptomenigitis	+	+	+	+	+	+	+	+	+	+	+	+
Necrosis of cortex	+	+	+	+	+	+	+	+	+	+	+	0
Thrombosed meningeal veins	+	+	+	+	0	+	+	+	+	+	+	0
Probable pathway :												
Direct extension		+	+	?	+		+	+	+	+	+	
Thrombophlebitis	+			?		+						

* Operative fracture through crista frontalis.
† Otitis media.
‡ Metastic from bronchiectatic abscess.

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ON THE SO-CALLED "LARYNGEAL EPILEPSY."

BY C. W. M. WHITTY.

Introduction.

Charcot (1876) first described two cases of a condition which he called "Vertige Laryngé." The presenting symptom was a slight cough followed by an attack of giddiness or actual loss of consciousness. A tickling sensation in the larynx would precede a slight dry cough, during which the patient would feel giddy and collapse, sometimes with loss of consciousness, during which clonic movements might occur. Both cases were men aged about 55 with no previous history of epilepsy and both had evidence of mild bronchitis or laryngitis. Charcot attributed the symptoms to a reflex irritation of the laryngeal nerves and likened it to the vertigo which Ménière ascribed to irritation of the 8th nerve in the inner ear. In support of this he mentioned a case described by Sommerbrodt (1876). Here a man, aged 54, with a history of hoarseness of voice for seven years, was found to have a laryngeal fibroma attached to the left vocal cord. Eight months after this discovery he started having attacks of loss of consciousness with clonic movements and tongue biting. These did not respond to bromides, and occurred as frequently as several times a day. Following removal of the growth the attacks ceased and had not recurred five months later at the time of this report. In this case there was no mention of cough preceding his attacks. This condition has since usually been called by the name "Laryngeal Vertigo" which Charcot gave to it.

Gasquet (1878) described a case in which an elderly man caught a cold and developed violent spasms of coughing. Later these spasms were followed by attacks of unconsciousness in which he fell down. He came round in two to three minutes feeling confused. These ceased following "treatment directed to his laryngeal affection."

Charcot (1879) reported two further cases in which coughing preceded loss of consciousness with twitching of limbs and face.

Leferts (1883) mentioned two cases in which slight spasmodic cough was associated with momentary unconsciousness or dizziness and confusion.

Gray (1882) recorded one case of attacks of momentary unconsciousness following severe cough in a man aged 55 who seventeen years previously had had an extra cranial bullet wound of his head.

Krishaber (1882) described a middle-aged man who at 25 had had

syphilis. He was in apparent good health when he had an attack of unconsciousness following a violent emotional upset. Next day he had a giddy attack following an attack of dry cough and later lost consciousness following a coughing bout. Following a similar attack on another day, he noticed coughing produced not complete loss of consciousness but slight mental confusion (étourdissement).

McBride (1884) gave a short review of this condition of laryngeal vertigo in which he discusses nine cases from the literature and adds one of his own. The patient, after swallowing a fish bone, used to get attacks of suffocation and giddiness. There is no mention of preceding cough or tickling in the throat, and McBride's reasons for including the case appear to be that it was cured by counter-irritation to the larynx. He discusses the ætiology of the attacks, which he suggests are due to cardiac asystole caused by expiration with closed glottis.

Massei (1884) described three cases in which coughing is associated with brief loss of consciousness or confusion. In one of his cases the attack was preceded by tickling in the throat and a desire to cough, but no actual coughing occurred.

Duavin (1887) himself suffered from attacks of unconsciousness preceded by tickling in the larynx and cough, and recorded two patients with similar symptoms.

Garel (1889) described a case where the sequence, feeling of tickling in throat, cough and loss of consciousness with clonic movements of limbs occurred. Here there was no abnormality found in the throat.

Cartaz (1890) described four similar cases, one of which appeared to be cured by cauterization of adenoid tissue.

Armstrong (1890) added a further case in which the attacks started a year after being "garrotted." In this case Armstrong tried out the effects of forced expiration with a closed glottis, but this did not induce an attack or its prodroma.

Huguin (1890) reported a case which he considered laryngeal vertigo, but there is no mention of cough preceding the attacks.

De Havilland Hall (1894) gave an excellent review of twenty-six published cases and a description of one of his own. He noted that twenty-one of the cases occurred in males and that disease of the respiratory tract is usually associated with the condition. He discussed briefly theories of causation, mentioning congestion of cerebral vessels, laryngeal reflex cortical irritation, epilepsy and cardiac asystole as possibilities.

Getchell (1896) reported two cases of his own and gave a detailed review of seventy-five other published cases. His two cases presented the usual

picture of irritation of the larynx, cough—slight or severe—and loss of consciousness with falling. In an excellent analysis of the other cases he emphasized the sex incidence—only four out of seventy-seven were females. He noted a laryngo-pharyngeal abnormality in fifty-three cases. Twelve he records as having an epileptic family or personal history, and ten others as of "nervous temperament." As to ætiology he remarks: "Congestion of cerebral vessels (due to coughing) may also cause syncope; but it will not cause it unless there is an existing disorder of the central nervous system."

Watson-Williams (1908) discussed the ætiology and mentions a case of his own. Here cough is not prominent, but the attacks were always produced by "pressure on the laryngo-tracheal region." It seems doubtful if this was a case of laryngeal vertigo.

Adams (1936) described a case in some detail where the attacks started following whooping cough in which the spasmodic cough persisted. This patient had no movements during the attack, but was muddled and sleepy afterwards. The attacks would follow one or two slight coughs, but he might have a violent bout of coughing with no attack. Attacks were always preceded by a tickling of the throat. There was no mention of epilepsy in past or family history. The attacks ceased following a submucous resection of a deflected septum.

Barber (1936) described a very similar case in which giddy attacks with or without momentary loss of consciousness were preceded by tickling in the throat and cough. This paper contains the first mention of carotid sinus syncope as a possible differential diagnosis. Barber dismisses it in these cases, as he notes that Ferris *et al.* (1937) make no mention of cough in their detailed analysis of the carotid sinus syndrome.

Thus it would appear that the condition is not excessively rare. It is interesting to note that no mention is made of it by Gowers (1907). Buzzard (1936) mentions it as a very rare condition and suggests it may be of an epileptic nature. It is not referred to in Wilson's (1940) textbook of neurology, while Brain's (1940) states briefly ". . . any stimulus causing syncope in one may cause epilepsy in another with no other predisposition to epilepsy. Such stimuli include cisternal, veni-, lumbar and pleural puncture . . . even coughing (laryngeal epilepsy)."

The reason for its apparent rarity in the neurological literature of this country would seem to be that, with a presenting symptom of cough, the cases are commonly referred to the laryngologist—a suggestion borne out by the bibliography. The omission of Charcot's original descriptions from

the first English translations of his work, an explanation suggested by Adams (1936) for this rarity, is scarcely likely to have misled so acute an observer as Gowers had he encountered a case.

Theories on the ætiology of the condition fall into two main groups. Those which regard it as primarily neurological and those which regard it as primarily cardiovascular. In the first group is Charcot's theory of reflex vertigo and the epileptic theory of origin; while in the second appear the theories of cerebral anoxæmia, venous congestion and cardiac asystole.

Whatever may be the cause, a consideration of the reported cases gives a clinical picture which is clear and consistent, although there may be individual deviations in some respects—sometimes sufficiently great to make the diagnosis improbable. The condition occurs in middle-aged males of plethoric type and is associated with a laryngitis or bronchitis. A previous personal or family history of epilepsy may occur, but is not common. The presenting symptom is an attack of dizziness or loss of consciousness preceded by a tickling sensation in the larynx and a cough which may be slight or severe. Epileptiform movements may occur during the attack, but a more constant feature is a slight mental confusion afterwards. About a quarter of the cases appear to recover or remit following local treatment of any abnormality which may be present in the upper respiratory tract.

In this paper four cases are described. In three of these it has been possible to make observations which may throw light on the mechanism of production of the seizures.

Case Histories.

(1) C. W. C., aged 47, a carpet merchant by trade, was sent for neurological opinion following a car accident under the following circumstances. He was driving his car at night when he met with an avalanche of oncoming headlights. Just then he remembers a fit of coughing started. The next he recalls clearly is being in a police-station and being put through various tests. In the interval he had had an accident and had run into a motor cyclist. He does not recall seeing the motor cyclist, the actual accident, or being asked to help just afterwards. He has only a confused memory of his journey to the police-station. Some seven years before this occurrence he had had an attack of laryngitis which left him with a permanent irritating cough. Sometimes the cough leads on to an attack of dizziness, and on at least three occasions he has lost consciousness and fallen during an attack. He comes round feeling confused as if he had been out for hours and feels "vacant" and not himself for two to three hours. The actual attacks are of momentary duration.

There was no family or personal history of epilepsy or fainting. He had had severe bronchitis as a boy and there had been suspicion of heart disease, for which he was first rejected and later accepted A1 for service in the 1914-1918 war.

On examination.—He was a stout plethoric man.

C.N.S.: No abnormal signs.

Digestive system: Normal.
Respiratory system: Chest emphysematous; otherwise normal.
Cardiovascular system: Retinal and peripheral limb arteries thick.
B.P.: 110/90. No other abnormality.
Urine: No albumin or sugar.

This was considered to be a case of laryngeal epilepsy. No observations on its future course were possible.

(2) W. O., aged 42, was referred to the Army Neurological Service complaining of occasional " black-outs " for the past two years. In civil life he was the manager of a bus company; in the Army he was acting as a driving instructor. He describes clearly four occasions on which he lost consciousness and fell down, following a bout of coughing. On each occasion the attack was momentary. There was no incontinence, tongue biting or history of movements during the attacks. On the last occasion he cut his head in falling. The attacks started in February, 1940. But for a period of ten months from July, 1940, he had no attack with loss of consciousness, although his cough continued and was sometimes followed by a " queer feeling " arising in the epigastrium and passing up to the top of the head—described as " numb tingling feeling," " bursting suffocating feeling." In both kinds of attack he feels momentarily confused and dazed and usually has a slight headache for one to two hours afterwards. His wife describes an attack. He starts coughing—not violently—suddenly he goes red in the face and slumps forward, or falls if he is standing. He seems momentarily unconscious. On coming round he seems dazed and does not answer questions sensibly for a few minutes.

There is no past or family history of epilepsy or fainting. The patient has had a chronic cough, worse in winter, for the past four to five years. No other illness. Smokes twenty cigarettes a day, drinks an occasional half-pint of beer. No neurotic traits elicited.

On examination.—He was a thick set, plethoric man. Height 5 ft. 7½ in., weight 14 st. 12 lb.

C.N.S.: No abnormal signs.
Digestive system: Normal.
Respiratory system: Some emphysema.
Cardiovascular system: Pulse 68.
B.P.: 130/80.
Apex beat: 3½ in. from mid-line in 5th space.
Urine: No albumin or sugar.

E.N.T. specialist reports: " Moderate hypertrophic rhinitis. Larynx very sensitive—appearance suggestive of chronic laryngitis."

Lumbar puncture gave a fluid of pressure 150 mm. and free rise and fall on jugular compression. It contained 30 mgm.% protein and 10 lymphocytes per c.mm.

W.R. was negative in blood and fluid. Blood count was normal.

X-ray of skull showed no abnormality. X-ray of chest showed some generalized congestion of the lung fields with basal emphysema.

An electrocardiogram was normal, as was also the electro-encephalogram, both at rest and after overbreathing.

In view of the possibility of coughing causing mechanical pressure of the collar on the carotid sinus and thus producing " carotid sinus syncope," digital pressure was applied in this region for a period of forty seconds on the right and seventy seconds on the left side. In each case a reduction of pulse-rate to about forty seconds occurred, which suggests that the pressure was affecting the sinus. But in neither case was there produced either an attack of unconsciousness or " queer feeling " in the epigastrum, described above.

The effect of passive venous congestions was tried. A sphygmomanometer cuff was put round the neck and inflated to 80 mm. pressure and held for one and a half minutes. There was marked cyanosis and venous congestion of the face, but no attack or "feeling." On several occasions the patient was induced to cough voluntarily for thirty to fifty seconds. On one occasion he stopped coughing and looked vacant for a moment. He said he had had a feeling in the pit of the stomach and so had stopped coughing. He denied loss of consciousness and answered questions sensibly immediately afterwards. The pulse was of good volume at the time. Cough could be readily induced with smelling salts in this man. But on no occasion did any attack occur.

Finally he undertook voluntary forced expiration with the glottis closed and maintained it for twenty seconds. The pulse slowed from 70 to 58 and the volume was much reduced. No cardiac asystole occurred and there was no attack or warning. Facial congestion was marked at the end of this.

This patient was advised to give up smoking, was given a simple sedative cough mixture to be taken when his cough was troublesome, and was put on to phenobarbitone, gr. 1½ nocte, gr. ½ mane. A follow up five months later showed that he still had occasional warning feelings, though no further loss of consciousness. These did not interfere with his work

(3) J. L., aged 33, a miner in civil life, was doing full cooking duties in the Army. He was referred for neurological opinion as he had momentary "black-outs" following coughing for the past two years.

He has had twenty to thirty attacks in which he gets a tickling in the throat causing a harsh, dry cough. "The cough seems to stop my breath"; he has a "pressure feeling" in his head and falls unconscious for one minute or two; comes round feeling momentarily confused. No history of incontinence or tongue biting. He has suffered several minor injuries. After an attack he commonly has a dull headache for about one hour. Witnesses speak of him going blue in the face during attacks. This patient states he can distinguish the cough which precedes these attacks from an ordinary cough—it is more dry and irritating and sometimes seems high pitched and may be preceded by tickling in the throat. Sometimes an ordinary cough will change its character and he will know he is going to have an attack. Immediately before an attack there is a sense of angor animi.

On one occasion he remembers a similar attack of unconsciousness with *angor animi* following a bout of hearty laughter. This is an isolated occurrence. He states that he can sometimes "fight off" an attack when he thinks it is coming on. In that case he will fall down as his legs give way and feel dizzy but not lose consciousness.

There is no past or family history of epilepsy or fainting.

He had a head injury with thirty minutes post-traumatic amnesia five years ago. For eight years or so he has tended to have a slight "winter cough." Apart from this his health is good. No neurotic traits elecited.

On examination.—A stocky, obese man. Height 5 ft. 8 in., weight 13 st. 2 lb. Mentally he is a quiet, stolid type who does not appear at all worried about his attacks.

C.N.S.: No abnormal signs.

Cardiovascular system: Pulse 56.

B.P.: 130/60.

Digestive system: Normal.

Apex beat: 3½ from mid-line in 5th space.

Respiratory system: Slight emphysema.

Urine: No albumin or sugar.

Lumbar puncture: Clear fluid. Press: No block. Cells 4 lymphocytes per c.mm. Protein 35 mgm.% W.R. negative in blood and fluid.

X-ray skull: Normal. X-ray chest: Increased basal striations both lung fields.

Electrocardiogram: Normal.

Electro-encephalogram shows irregular medium voltage. Six per second waves of constitutional type. This record is suggestive of epilepsy.

E.N.T. opinion: "Some congestion of right airway, otherwise nil abnormal."

Carotid sinus pressure caused a reduction of pulse-rate from 54 to 38 on the right and from 52 to 44 on the left, but produced no attack or other feeling than slight local constriction. Forced coughing, constriction of neck at 90 mm.Hg. for two minutes and at 110 for thirty seconds and forced expiration with closed glottis all produced no attack or warning, though the latter two procedures caused evident facial cyanosis and venous congestion.

He was given phenobarbitone gr. 1½ nocte. gr. ½ mane. and during a six-week period of observation he had no attacks. No follow up was possible in this case.

(4) H. B., aged 47, was a heavy lorry driver in civil life and driving instructor in the Army. He was referred for neurological opinion on account of attacks of dizziness for about one year.

About eighteen months ago he noticed he was unduly short of breath—mild exertion would make him dyspnœic. Six months later he noticed giddy attacks. They would occur at any time of day, usually when he was standing up—a tingling feeling all over his body with blurring of vision and sometimes definite diplopia leading to a "dizzy giddy feeling," so that he had to sit down or he would fall. There was no relation to exertion. The attacks occurred spontaneously, but he has also noticed that they might follow a bout of coughing induced by a tickling feeling in the larynx. They occurred about two to three times per week. On three occasions he has actually lost consciousness during an attack and fallen down. He is out for about two minutes. There is no history of incontinence, tongue biting or movements during the attack. He feels dazed and muddled for a few moments on coming round and usually has a headache for one and a half to two hours afterwards. Of these three occasions, two were preceded by an irritating and rather violent cough. The third appeared spontaneously. No personal or family history of epilepsy or fainting. He has suffered from a chronic "winter cough" for ten years now. Otherwise past health excellent. No neurotic traits elicited.

On examination.—Thick-set, plethoric man. Height 5 ft. 8 in. Weight 13 st. 10 lb. Slight tendency to cycanosis. Rather worried about his attacks, but he appears easily reassured. He is of fair average intelligence and appears a reliable witness.

C.N.S.: Fundal vessels rather thick. Otherwise normal.

Cardiovascular system: Pulse 68. Peripheral limb vessels palpably thickened.

B.P.: 160/100

Apex beat: 3½ in. from mid-line in 5th space.

Respiratory system: Some emphysema.

Digestive system: Normal.

Urine: No albumin or sugar.

Lumbar puncture: Clear fluid. Pressure 140 mm.Hg. No block. Protein 40 mgm.%. Cells 4 lymphocytes per c.mm. W.R. negative in blood and fluid.

X-ray skull: Normal. X-ray chest: Increased striations, both lung fields suggesting slight bronchitis. Heart shadow normal.

E.N.T. opinion: No abnormality of nose or throat.
Blood count: Normal.
Electrocardiogram: Normal record.

Carotid sinus pressure reduced pulse-rate from 68 to 44 and in forty seconds reproduced the aura of "giddiness and dizziness," but without loss of consciousness. Constriction of the neck at 90 mm.Hg. for forty-five seconds caused very marked venous congestion and an aura. It should be noticed that during carotid sinus pressure there was definite cyanosis of the face. Forced expiration with closed glottis had no effect; but on one occasion, while coughing, the patient paused during the bout, went blue in the face and for a moment did not answer questions. He denied loss of consciousness afterwards, but had a slight headache for about an hour.

He was put on phenobarbitone gr. 1½ nocte. gr. ½ mane. and during a three weeks' observation period had only one mild attack without loss of consciousness. No further follow-up was possible.

All these four cases are well covered by the general description of laryngeal epilepsy or vertigo given earlier. The sex and age incidence, the bodily habitus and respiratory disease are all appropriate. They will be discussed in detail later.

Discussion.

It is evident that the proximate pathology for loss of consciousness must be sought for in the brain. As Gowers (1907) argues, the epileptic attack and cardiovascular syncope must have a common meeting place in the brain, and to that extent the condition described in this paper is neurological. But when we consider the more remote factors in the causation of unconsciousness, we may see that one cause—for instance, cerebral ischæmia—may have a clear-cut cardiovascular pathology, while the sudden loss of consciousness of certain epileptics with no apparent change in vasomotor state would appear to be primarily a mechanism of the central nervous system *per se*.

But the leaven of Gowers' inquiries as to where exactly we can draw the line between an epileptic fit and the simple faint is still working. When we find evidence of cases where the most trivial stimuli cause fainting, and when these syncopal attacks occur frequently, then, even if there is evidence of a cardiovascular component in the causation, we may legitimately ask whether there is not also some primary abnormality of the central nervous system. This was Getchell's (1896) view in considering the specific problem of the ætiology of laryngeal epilepsy. It is echoed in Cobb's (1932) discussion of the causes of epilepsy. Here he attempts to educe certain simple proximate mechanisms in the production of convulsions—two of which he postulates as impaired neuronic conduction and anoxæmia. But he further points out that even in traumatic epilepsy, where regional brain

damage can be reasonably inferred, the incidence of epilepsy in the relatives is higher than in a control group, which suggests some inherent abnormality in neurological constitution.

There is further evidence from a study of electro-encephalograms in those who faint easily or have an occasional unexplained "black-out," or perhaps have had "convulsions" from some trivial cause in infancy, the incidence of abnormal electro-encephalograms of a type which is indistinguishable from that found in certain epileptics is higher than in normal controls (Williams, 1942). Moreover, in those cases where epileptic convulsions are proven, the amount of such a stimulus as hyperventilation or water retention (as in the water-pitressin test) needed to produce abnormal cortical potentials may vary from one case to another. Thus the evidence is in favour of a component of primarily neurogenic abnormality in all those cases that lose consciousness readily. The component may be large as in the established idiopathic epileptics with a heavily tainted family history or slight as when altitude flying or the violent stimulus of the complete cardiac asystole of Stokes-Adams syndrome may be needed to produce an attack. All brains would presumably produce convulsions if they were subjected to such a stimulus as electrical shock "therapy." So that the question of whether the difference between "epileptic" and "normal" brain is of kind or degree is still debatable. But it is evident that within the sphere of "epilepsy" there are gradations of abnormality. Moreover, the epileptic seizure as Cobb (1932) puts it "must be looked upon as a *symptom* entirely analogous to the symptom of headache."

With these considerations in view some points of interest emerge from the investigations of the cases reported here. In one of them (J. L.) there is evidence, both clinical and electro-encephalographic, that his condition was epileptic. He had had at least one attack unassociated with coughing and he had abnormal cortical potentials. If the condition was primarily epileptic, the question still remains of the part played by cough in the seizure. It seems unlikely that it acted by producing a cerebral anoxæmia, as the artificially produced congestion by coughing and constriction of the neck did not do so. There was no discoverable laryngeal abnormality. Moreover, prolonged voluntary coughing produced no attack: facts which are against Charcot's theory of a reflex arising from the larynx. Finally the patient himself distinguished between an ordinary cough and the cough which preceded an attack—it had a subjectively different quality, was drier and more irritating. In this case it would fit the facts reasonably to regard the cough and any laryngeal sensation preceding it as essentially the aura of an epileptic convulsion.

In C. W. C. and H. B. there was evidence of some arterial degeneration. This condition, if it extended to cerebral vessels, would favour the development of convulsions by such factors as anoxæmia, &c. But in H. B. it is particularly interesting to note his seizures occurred both with and without cough. Moreover, other methods of producing cerebral anoxæmia also produced the "warning" of his attacks. Here the factor of anoxæmia produced mechanically by coughing would seem to have aided, at any rate, in the production of a convulsion, but in a brain already predisposed. Although there was no electro-encephalogram here, the clinical evidence of the epileptic nature of the attacks—the sudden clouding or loss of consciousness, the brevity of the attack, the recovery with confusion and the headaches afterwards—was convincing.

Finally in the case of W. O. the attacks have many features suggestive of epilepsy—rapid onset of unconsciousness of brief duration, recovery with confusion and headaches afterwards. Moreover, the results of venous constriction and forced expiration with closed glottis argue against cerebral venous congestion as a causative factor. It is possible that here, too, the cough might be part of an aura. But the fact that a clear epigastric aura sometimes follows the coughing attack without complete loss of consciousness makes this unlikely. Further, this man had a definite laryngitis, a factor noted in some of the earlier cases. The case would therefore seem to fit best into the category of true reflex epilepsy; an afferent stimulus from the diseased larynx passing up the laryngeal nerves to produce a cerebral effect in the way that Charcot originally suggested. In support of this it may be noted that prolonged voluntary forced coughing produced an aura on one occasion.

Thus in these four cases three possible mechanisms for the production of the seizures emerge, despite the similarity of clinical picture. In none of these cases was there any evidence that an abnormal carotid sinus reflex played a part in their production. But in at least one case in the literature, that of Watson-Williams (1908), the attack—produced constantly by pressure over the laryngo-tracheal region—was most probably a "cerebral" type of carotid sinus syncope.

In other published cases a similar diversity of ætiology is likely. But the factor of epilepsy seems to appear in most of them and laryngeal epilepsy seems a more satisfactory name for the condition, since true vertigo rarely, if ever, occurs.

Some of the cases reviewed were almost certainly not laryngeal epilepsy. Thus the evidence in Huguin's (1890) case is quite inconclusive. Krishaber's

(1882) case would also appear to be doubtful. Apart from the association of cough and loss of consciousness, the patient was also known to have attacks due to emotion and due to loud noises. Watson-Williams' (1908) case has already been mentioned and McBride's case will hardly qualify. Sommerbrodt's case is of special interest, as the successful removal of a local laryngeal condition appeared to effect a cure. This case would be explained very adequately on the basis of a true reflex laryngeal epilepsy. Although anoxæmia may have played a part, it seems unlikely to have been a large one as Sommerbrodt specifically mentions that interference with breathing was slight.

Conclusions.

It seems reasonable to postulate a small group of cases of epilepsy in which the epileptic attack immediately follows on coughing. In this group there is usually an associated chronic laryngitis or bronchitis. In four cases, seen personally, all were of a pyknic bodily habitus. In all four cases there was no past or family record of epilepsy.

Of the ætiological theories proposed to account for laryngeal epilepsy, some may be dismissed as improbable. Thus the idea that forced expiration with the closed glottis will produce asystole and convulsions is not borne out by the four cases investigated above, and in Armstrong's (1890) case also this manœuvre failed to produce either asystole or an attack. Weber's original observations in this connection (quoted by McBride, 1884) were made on animals and under conditions unlikely to be reproduced clinically. That cerebral venous congestion and anoxæmia due to coughing is a cause, without any other cerebral abnormality, is also unlikely; for venous constriction—with engorgement greater than that produced by violent coughing—failed to produce an attack in the man W. O. in whom forced coughing did actually produce an aura. Moreover, in another, H. B., in whom venous obstruction did produce an aura, the attacks occurred at times independently of coughing.

The majority of cases would appear to be primarily neurogenic: either a true reflex laryngeal epilepsy as in W. O. or Sommerbrodt's case and in four of Charcot's, or epilepsy with a laryngeal aura as in J. L., or finally venous congestion caused by violent coughing but in a patient with a cerebral cortex predisposed, whether by vascular degeneration or other factors, to epilepsy.

Summary.

(1) A condition described originally by Charcot as laryngeal vertigo is reviewed and early theories of ætiology mentioned.

(2) Four cases are reported in detail.

(3) A review of the ætiology of the condition is given and the bearing of investigations made on the four reported cases is considered. It is suggested that the condition is primarily epileptic. The name laryngeal epilepsy would appear more suitable than that under which the condition is at present most widely known.

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GENETIC AND FAMILIAL ASPECTS OF DYSTROPHIA MYOTONICA.

BY OTTO MAAS AND A. SPENCER PATERSON.

INTRODUCTION.
FREQUENCY.
AGE AT ONSET.
AGE AT DEATH.
FERTILITY.
MISCARRIAGES AND DEATHS IN INFANCY.
FREQUENCY OF TWINS.
SOCIAL POSITION.
SEX INCIDENCE.
PERSISTENCE OF THE DISEASE THROUGHOUT SEVERAL GENERATIONS.
PROBLEM OF TRANSMISSION THROUGH UNAFFECTED PERSONS.
TRANSMISSION THROUGH MALE AND FEMALE.
THE PROBLEM OF WHETHER DYSTROPHIA MYOTONICA RESULTS FROM ONE SINGLE FACTOR.
PROGRESSIVE DEGENERATION AND REGENERATION.
FRATERNAL PROGRESSIVE DETERIORATION.
CONCLUSION.

THE purpose of this paper is to discuss the familial aspects of dystrophia myotonica, including the mode of transmission and symptomatology in successive generations. The subject matter includes myotonia congenita (Thomsen's Disease) and paramyotonia, since we have shown in a previous paper (1939) that these conditions occur in families affected by dystrophia myotonica, and are in our opinion essentially the same disease.

In this connection it may be noted that Kinnier Wilson in his posthumous work "Neurology" (1940), while believing that there was a difference between dystrophia myotonica and myotonia congenita, yet maintained that muscle atrophy could occur in the latter disease. He stated that only when cataract and other signs of degeneration were observed should dystrophia myotonica be diagnosed.

Despite our respect for Wilson's views, we believe that our arguments are valid. There does not appear to be any advantage in classing as a separate disease those cases with myotonia alone or with myotonia and wasting alone. We could not be confident that these patients would not develop other symptoms such as testicular atrophy or cataract, any more than we could say that members of affected families with cataract alone would not develop myotonia.

Frequency of the Disease.

Not uncommonly a symptom-complex has been thought rare when first recognized, but has later been found to be relatively frequent. Harvey Cushing (1933), for instance, wrote that acromegaly, which was once considered rare, was later found to be quite common when looked for in a mild, yet unmistakable form. This state of affairs is especially likely to occur when variants of a disease have erroneously been separated as different entities. In this disease where the disorder is to some extent polymorphic in its manifestation, expressing itself in one member of a family essentially as mental defect, in another as cataract and in another as severe myotonia with wasting, it is important to recognize the disorder in all its forms, even where the wasting and increase of tone are relatively slight.

Some years ago the condition was considered uncommon. Rouquès (1931) collected about 200 cases in the literature. At the National Hospital, Queen Square, between 1933 and 1938, only 29 cases of dystrophia myotonica and Thomsen's Disease were diagnosed as compared with 76 cases of myopathy. Yet in the last decade a number of writers have recorded their conviction that this disease is not a rare one. (A. Vogt (1931), A. Ravin (1939), Kinnier Wilson (1940), Waring, Ravin and Walker (1940).)

In the present series the families of 94 patients have been examined, and 261 individuals have shown definite signs of the disease. Further, there were 286 other members of these families affected by more or less suspicious symptoms. It would appear, therefore, that the condition is not so uncommon as was at one time supposed.

Age at Onset.

It was once thought that myotonia congenita, as its name suggests, was present from birth, whereas dystrophia myotonica came on in the third or fourth decades of life.

Signs of the latter disease, however, were observed at the ages of 6 and 14 by Frey (1926), while Boeters (1935), A. Hauptmann (1919), Grund (1911), Henke and Seeger (1927) and other authors reported similar cases. We have observed cases aged 14, 12, 9, 8, 6, 5, 4 and 3. Definite signs found in infancy are in fact not uncommon, but lay people do not notice them. The illness is dated by them from the time when weakness, stiffness or cataract have necessitated medical advice.

Age at Death.

Fleischer (1918) stated that those affected by dystrophia myotonica usually died about the age of 50. A. Vogt among others has found that

milder cases live much longer. We have found such patients comparatively well, although beyond the ages of 60 and 70.

Fertility.

It is difficult to assess how far fertility is adversely affected. If we compare in normal people the size of family of an earlier generation with that of the present generation, we shall be comparing a completed generation with an incomplete one, so that we shall expect *ceteris paribus* that the later family will be smaller. Again, as the size of family in the present generation among the general run of the population is greatly reduced owing to birth control measures, among other causes, we shall expect in any case that the later families in this series will also be reduced in size.

There are factors other than gonadal atrophy to be considered. Muscular disease and cataract will make it more difficult for the male to earn his living or for the female to marry. Poverty will increase infantile mortality. Endocrine abnormalities such as diabetes and goitre, not uncommon in these families, may further reduce fertility.

When such facts are borne in mind, the accompanying Table I may be better evaluated. In the upper table, the parents had either been examined and found normal or else reported normal. They therefore included a large number of unaffected persons as well as some who were affected but not diagnosed. In the lower table one parent in each case was severely affected. It is striking that the first group had an average of over five children while the second group had 1·38.

Table I.—Showing the Difference in Number of Offspring of the First Examined Generation and the Offspring of Severe Cases.

1.—Offspring of parents reported or found to be normal.

Number of sibships.	Children alive after infancy.
89	458

or 5·14 children per sibship.

2.—Offspring of severe cases of dystrophia myotonica.

Number of sibships.	Children alive after infancy.
108	153

or 1·38 children per sibship.

A number of individuals indeed became impotent at an early age, the testes being soft and atrophied. It was found that on the whole impotence co-existed with a marked degree of myotonia and wasting.

Those families, however, where for the most part symptoms were only slight, were often remarkably prolific.

Miscarriages and Deaths in Infancy.

Since on the whole we are dealing with the poorest section of the population, it is difficult to estimate how far the undoubtedly high incidence of miscarriage and infantile mortality is due specifically to the disease and how far to poverty. Henke and Seeger (1927) inclined to the latter explanation, Frey (1926) to the former.

Since impotence is directly attributable to the disease and since the endocrine system in general is so frequently abnormal, it seems reasonable to attribute the unduly large number of miscarriages and infantile deaths directly to the disease process. When our material is further analysed to establish whether miscarriages occur with equal frequency, no matter whether the father or mother is affected, this will throw more light on the problem.

Frequency of Twins.

During the time that the clinical material under investigation was accumulating, the question of whether twinning was more frequent in these families was not especially considered. The impression, however, gradually grew that multiple births were being recorded with unsual frequency, and this led us to examine the literature on the subject. Only a few comments appear to have been made on twins occurring in such families by other writers. Magneral (1904) reported that twin sisters of a patient had died very young. W. A. Schmidt (1919) reported triplets in an affected family. Fleischer (1922) observed two brothers belonging to an affected family, both of whom were the fathers of twins. Frey (1926) reported a patient who was the father of two pairs of twins. Both of the first pair died shortly after birth. One of the second pair was healthy, while the other was affected by cataract (whether uniovular was not stated). Boeters (1935), reporting on twenty affected families, mentioned eleven pairs of twins in seven different families. All of these were binovular. In four families two pairs of twins were found. Henke and Seeger (1927), however, mentioned that in comparing non-affected branches of the family examined with normal families the proportion of twins was the same in each case, namely, 1 per cent.

Studies of myotonia congenita also only rarely comment on the frequency of twin births, although in fact they appear to occur frequently. Pantoppidan (1884) reported a male so affected, while his twin sister was healthy. Liebenam (1939) examined a sibship of seven. The sixth and seventh were twins, both affected. The eldest of this sibship, a female, was the mother of twin brothers.

TABLE II.—TWINS.

No. of the family in this series	*Place of the Twins in their Sibship*	*Observations on the Sibship of the Twins*	*Observations on Parents and other Blood-relatives*	*Fate of the Twins*
1	5th & 6th of 6	Many suspicious	Mother suspicious, brother and sister of mother severe cases	Both suspicious when examined at 6 years
2	6th & 7th of 7	Several have cataract	Late mother : cataract. Numerous relatives severe cases	Miscarriage
6	2nd & 3rd of 3	The eldest in this sibship died of brain-tumour in infancy	Father, suspicious. Father's mother and relatives severe cases	Healthy in early infancy
12	7th & 8th of 9	One brother and one sister severe cases	Father (dead) was affected, as reported	Died at the age of a few weeks
12	7th & 8th of 8	No examination	Father third cousin of the original patient	Both died in infancy
12	1st & 2nd of 2	No examination	Mother distant cousin of the original patient	One died at 10 months, the other not available
12	2nd & 3rd of 6	The fourth, suspicious	Mother, a cousin of the original patient, suspicious	Examined at 52 years. One suspicious, one normal.
25	5th & 6th of 7	Several affected	Mother has cataract	One, a girl, died at 8 months, one, a boy, healthy at 18 years
20	1st & 2nd of 2		Mother affected	A girl died at birth, a boy, affected
26	7th & 8th of 9	Sister affected	Late father had a cataract	Miscarriages
56	1st & 2nd of 2		A brother of the mother had affected sons	No report
60	1st & 2nd of 2		Father dead. Mother healthy	Girl affected, twin brother killed in action
61	5th & 6th of 8	Several suspicious	Father, suspicious. Father's brothers affected	Alive at 11 years, not examined
76	1st & 2nd of 2		Mother suspicious. Brothers of mother's father affected	Miscarriages at 3 months interval. Doctor said they were twins, both were well developed
72	1st & 2nd of 2		Father suspicious. Two sisters and one brother of the father affected	One died at birth, the other healthy at two years
90	3rd & 4th of 4		Father, suspicious. Brother of the father affected	Both girls healthy at four years
93	8th & 9th of 12	Several affected		A boy was killed in the war at 19 years, his twin sister died, unmarried, at 24 years

It is noteworthy that twins were born with surprising frequency in Dr. Thomsen's family, although neither Thomsen (1876) himself in his original paper nor Nissen (1923), who later published observations on this family, commented on the frequency of twins. As shown by Table II in Nissen's paper, Dr. Thomsen himself had two sisters who were twins, one of them affected. The unaffected one became the mother of four sons, two of whom were twins. One of these again was the father of two pairs of twins. A stepsister of Dr. Thomsen, herself affected, had several children, one of whom became the father of twin girls. Another stepsister of his became the mother of a son who procreated twin girls. Thus there were six pairs of twins among a very small number of his near relatives.

Table II gives a list of the twins reported in the present series. If special care had been taken from the outset to inquire after twins, even more facts might have been reported, especially with regard to whether they were uniovular or binovular. The percentage of twin births is of some interest from the biological standpoint, and if it could be definitely ascertained, it would throw light on whether the noxa to the germ-plasm predisposes to twinning. It might, however, be misleading to give the percentage of twin births in our series, as we almost certainly missed a large number. Nevertheless it did appear that in 728 confinements, 14 were twin births, or 1·92 per cent. Newman (1942) states that the figure for the U.K. is not known, but that the percentage for American whites is 1·15.[1] There is therefore some indication that myotonia, especially under certain conditions or in certain families, predisposes to multiple births.

Social Position.

Some writers have maintained that nearly all affected families belong to the poorest section of society, erroneously attributing the mental backwardness found in so many cases to this cause. In fact, however, mental enfeeblement is caused by the disease, and this leads to the steady descent of such families in the social scale, as exemplified by the family of four generations described by Caughey (1933), which has descended from the sister of a world-famous general and politician who was himself only mildly affected. There was a steady decline in intelligence and social position. Among A. Vogt's patients, however, were persons of high rank, while the present series includes the families of a distinguished writer and an artist of wide repute.

[1] E. Slater (1941) mentions 1·158 ± 0·503 as the figure for psychotics as a whole.

This disease, therefore, except in its severe form, is not incompatible with intellectual distinction.

Sex Incidence.

As demonstrated by one of us (O. M., 1937), a significantly greater incidence of severe cases occurs in the male sex, but a greater frequency of mild and doubtful cases in the female sex. This result has been confirmed by subsequent investigation (*see* Table III). As was to be expected, however, there were some exceptions to this, females being more seriously affected, especially if they came at the end of a sibship. Sometimes the severe case in one generation was a female and in the next a male.

T. A. Fraser Roberts (1940, p. 221) has said that "in most instances (of hereditary disease) it is the male which shows the higher frequency of expression."

Persistence of the Disease Throughout Several Generations.

Like other writers, we examined numerous families in which several generations were affected by dystrophia myotonica. The view that dystrophia myotonica in its complete form usually affects one generation only (Ravin and Waring, 1939) has not been confirmed by the present series. Twenty families had one member markedly affected in both the first and second generation. In numerous other families it appeared very likely that two, three or even four generations were affected by definite signs of the disease. Further it has been remarked by several writers how frequently stepbrothers and stepsisters are affected (F. v. Soelder (1895) on paramyotonia, Boeters (1935), Maas (1937), S. Kolb, A. M. Harvey and M. R. Whitehill (1939)). It is therefore certain that the disease is transmitted in a dominant manner, though not as a simple dominant, as will be shown later.

Problem of Transmission Through Unaffected Persons.

It has been held that where a disease is transmitted as a dominant, persons who are themselves unaffected cannot transmit the disease. Others, however, have maintained that such a disease could in fact skip a generation. A. Biemond (1928) for example, relying on a pedigree published by Heringham, maintained that a generation was skipped in a family affected by Charcot-Marie-Tooth's Disease.

O. Maas (1937) collected instances leading one to suspect that this might occur in dystrophia myotonica. The evidence, however, was inconclusive. Recently we examined one of Dr. A. Feiling's patients (Fam. No. 71), whose children, as well as a sister and her daughter, were affected

by definite signs of the disease, while the man himself had only a rather longish face, wasted temporal muscles, doubtful facial weakness and doubtful myotonia in his tongue and quadriceps. Again, a case of Mr. E. Wolff (Fam. No. 89) showed unmistakable signs of the disease, while her father, aged 56, and her mother, aged 54, felt perfectly healthy. Neurological examination revealed nothing abnormal either in the father or in the mother, until Mr. Wolff found a mild but typical cataract on slit-lamp examination of the mother.

It appears, therefore, that while the manifestation of the disease may be very slight in a carrier, transmission of dystrophia myotonica through

TABLE III.—CASES OF DYSTROPHIA MYOTONICA EXAMINED UP TO JULY 1, 1940.

	Male	*Female*
Severe	97	50
Mild	50	64
Suspicious	130	156
	277	270

There is a significantly greater number of severe cases among the males, and suspicious cases among the females.

completely unaffected individuals has been very doubtful up to the present, and should not be assumed without electrical examination of the muscles and slit-lamp examination of the lens.

THE PROBLEM AS TO WHETHER DYSTROPHIA MYOTONICA IS TRANSMITTED MORE FREQUENTLY THROUGH MALE OR FEMALE.

Table IV shows no marked difference as between the two sexes for the transmission of dystrophia myotonica. Thus 34 men, who were definitely affected, had 45 offspring with definite signs, while 28 definite female cases had 39 children unmistakably affected.

TABLE IV.—TRANSMISSION OF DYSTROPHIA MYOTONICA.

		No. of propositi	*Offspr. def. case*		*Offspr. suspic.*	
			M.	*F.*	*M.*	*F.*
	A.—From *male* propositus					
I.	Prop. exam., def. case ..	34	26	19	20	21
II.	Prop. report, def. case ..	9	13	9	1	3
III.	Prop. exam., suspic. ..	17	2	2	19	18
IV.	Prop. report, suspic. ..	23	26	27	12	18
	Total	83	67	57	52	60
	B.—From *female* propositus					
I.	Prop. exam., def. case ..	28	17	22	10	13
II.	Prop. report, def. case ..	3	1	4	5	3
III.	Prop. exam., suspic. ..	27	9	9	19	28
IV.	Prop. report, suspic. ..	16	10	13	11	14
	Total	74	37	48	45	58

The Problem of Whether Dystrophia Myotonica Results from One Single Factor.

In the case of dystrophia myotonica, some writers have concluded that the disease results from involvement of a single factor which is dominant; that the frequency of the disease approaches the required proportion of one affected to one unaffected, sufficiently closely to justify this supposition, and that in those cases where some cardinal symptom such as cataract or myotonia is missing in a member of an affected family, this is to be explained by the supposed action of some modifying gene. Such a view has been held by Ravin and Waring (1939), partly on the findings of Henke and Seeger (1927), whose results are given in a later section. After taking into consideration the available literature on the subject, they concluded that their figures justified the supposition of unifactorial transmission. That the problem is a difficult one may be seen if we give here a précis of some opinions of recent writers on the subject.

Schulz (1936, p. 213) pointed out the danger of using sibships collected from the literature, as was done by Henke and Seeger. Naegeli (1917), quoted by them, said that the fact that the disease in each case usually presented very similar symptoms argued for unifactorial transmission. This dubious statement that the clinical picture tends to be uniform will be discussed later.

B. Fleischer (1923), who had examined Henke and Seeger's material at an earlier date, doubted whether the facts could be explained on the basis of simple dominance, because the proportion of affected to unaffected was too high. Boeters (1935, 1936), as also Curtius (1939), however, believed that the proportion was near enough 1 : 1 to justify the hypothesis of simple dominance.

Ravin and Waring (1939), on finding that the proportion was higher than 1 : 1, supposed that the result was "probably explained by the error inherent in small numbers and by the selection of material which results, because the greater the number of affected individuals in a sibship, the more apt the sibship is to come under observation. If those cases labelled suspicious are concluded to be unaffected, the percentage of affected individuals in the families studied by Maas (1937) is 60." This view will be discussed later.

A. Vogt (1921, 1924, 1931), however, pointed out that different symptoms in this disease could be transmitted as separate affections, in some cases for instance the muscles not being affected. On these grounds he denied the existence of simple dominance.

J. Bauer and B. Aschner (1925) considered that the disease resulted from a combination of multiple factors, saying at first that they were linked, but later (1938) not insisting on this.

L. S. Penrose concluded from pedigrees published by O. Maas (1937, p. 515) that more than one factor was involved.

Scope of the Present Inquiry.

In order to ascertain whether one or more factors are involved in the transmission of this disease, attention must be paid (1) to the collection of statistical facts. A sufficiently large material must be forthcoming. In this series we examined 356 as against 114 examined by Henke and Seeger, who included an additional 78, about whom they had only hearsay evidence. We had to see that our material constituted a fair sample of the disease and in assessing the proportion of affected to unaffected, we had to exclude the original patients (propositi) in accordance with Weinberg's method.

(2) On the clinical side we had to decide on the significance of "suspicious cases." If these were different from normal cases, then their existence would argue against simple dominance, because of tending to increase the proportion of affected to unaffected cases.

We propose then to examine first whether the proportion of affected to unaffected cases is very much more than 1:1, and to see that these findings are not vitiated by statistical fallacies (paucity of material, selection of cases), nor by doubtful clinical methods (diagnosis by subjective impressions). If we can do this, then we shall have shown that the hypothesis of simple unifactorial dominance is not justifiable.

Secondly we propose to show that cases in which cardinal symptoms such as myotonia or cataract are absent are not infrequent. If it can be shown that the disease is not "almost monotonous in the uniformity of its symptoms," this would make the supposition of multifactorial transmission more likely.

The Proportion of Affected to Unaffected Cases.

Those who maintain that the proportion of affected to unaffected cases is about 1:1 in this disease generally quote Henke and Seeger's figures.

Dystrophia myotonica.	Presenile cataract.	Suspicious for dyst. myotonica.	Normal on examination.	Reported normal.
73	11	15	15	78

Counting suspicious cases as affected, they concluded that the proportion of affected to unaffected was 99:93, or 1·03:0·97.

The objections to these figures are that the number of those reported normal by "reliable laymen" is practically worthless. As Denny-Brown and Nevin (1941) say: "We agree fully with Adie and Greenfield (1923) that many patients in whom myotonia can be demonstrated objectively never had subjective symptoms."

Secondly it is characteristic of this disease that it usually becomes manifest at any time from the third decade onwards. It is therefore inevitable that those labelled normal should include a number which will become affected at a later date. Only if a generation which is already completed (i.e. in which all the members are deceased) is considered will such cases be excluded. This is, of course, generally impossible in practice, but this consideration shows that we are as a rule more likely to underestimate than overestimate the proportion of affected to unaffected cases.

Also it is now possible to diagnose cataract with precision with the slit-lamp, and myotonia with an electrical examination. In this way some cases previously classed as doubtful are later included among those definitely affected. Such patients, however, would have been missed by Henke and Seeger, who did not use either of these forms of examination.

Table V shows our findings after examining 356 members of such families. It will be seen that 236 were affected, 103 were suspicious and only 17 unaffected.

These 97 sibships examined belonged to families who, as far as we knew, were unrelated. These facts should dispose of certain statistical objections made regarding such material. Firstly our material is greater than that of Henke or Seeger; secondly the fact that so many propositi were investigated ensured that a fair sample of the disease was examined. There is no question of many interrelated persons connected with one original patient coming under notice from the very fact that they are an exceptionally affected family. Thirdly, it will be seen from Table VI that even when the propositi are not included among affected cases (following Weinberg's method) the number of affected to unaffected cases is still far in excess of 1 : 1, being in fact 139 affected, 17 unaffected, while 103 are suspicious. (Like Henke and Seeger, we neglected all those who had died before examination was possible.)

Again when we examined the offspring of 61 individuals affected by dystrophia myotonica, we found that 94 were definitely affected, 60 were suspicious, but only 22 were unaffected. Twenty-two of the suspicious cases and 11 of the unaffected were below the age of 20, so that many of these would become affected at a later date. Further, when we examined

the offspring of 27 severe cases, we found 47 affected, 19 suspicious, but only 4 unaffected.

TABLE V.—SIBSHIPS IN WHICH AT LEAST ONE MEMBER WAS DEFINITELY AFFECTED.

Number of persons examined in each sibship	*Number of sibships*	*Number of live births*	*Abortions No.*	*Died in infancy*	*Died later not examined*	*Alive, not examined*	*Unaffected*	*Suspicious*	*Affected*
2	30	121	11	17	25	10	5	9	46
3	22	118	4	17	23	7	2	17	46
4	22	160	3	37	20	11	5	30	52
5	11	73	5	7	7	0	4	15	36
6	5	53	4	7	9	3	0	16	14
7	3	28	0	5	1	1	0	4	17
8	2	16	0	0	0	0	0	5	11
9	1	11	2	0	0	0	0	3	6
13	1	15	0	2	0	0	1	4	8
	97	595	29	92	85	32	17	103	236

TABLE VI.—WEINBERG'S "PROBAND" METHOD.

Size of sibship (excluding those not examined)	*Number of propositi*	*Brothers and Sisters*		
		Affected	*Suspicious*	*Unaffected*
2	30	16	9	5
3	22	24	17	2
4	22	30	30	5
5	11	25	15	4
6	5	9	16	0
7	3	14	4	0
8	2	9	5	0
9	1	5	3	0
13	1	7	4	1
	97	139	103	17

Note.—This table is based on Table V. In each sibship one affected patient is treated as a "propositus" and not counted as affected.

THE SIGNIFICANCE OF "SUSPICIOUS" CASES.

When we examined a series of members of myotonic families, we found that a large proportion of those who did not show the typical syndrome were distinguishable from the completely normal by certain symptoms, such as abnormally weak grip, absent reflexes or some degree of mechanical myotonia. An apathetic myotonic facies with slight ptosis and wasting of temporals or asymmetric wasting of the sternomastoids were also common.

An account of the following family will give a good idea of the significance of "suspicious" cases.

Irene B. (Fam. No. 32) was a severe case, an in-patient at the National Hospital under Dr. Gordon Holmes in 1934. Irene was the second of six sibs, of which the eldest had died in infancy, while the youngest was an idiot, with severe muscle symptoms. The fifth, a male aged 27, felt healthy, but on examination was found

to be a definite, though mild case. One "suspicious case" was the fourth, a girl who had a pinched myopathic facies. As she was mentally affected, a detailed physical examination was not possible. The other "suspicious" case was the third, who, when first examined on March 17, 1935, said she was healthy. We discovered, however, wasting and weakness of the facial muscles, doubtful wasting of the sternomastoids and suspicious myotonia in the tongue. At that time she was labelled "suspicious." On re-examination, however, on January 1, 1939, she complained of stiffness of the hands, and there was marked wasting and weakness of the face with definite wasting of the sternomastoids. Myotonia was definite in the tongue, right thenar muscles and extensors of the forearm. Arm reflexes were absent and the diagnosis appeared to be certain.

It will be seen that this family, not at all an unusual one in this disease, showed one infantile death, one low-grade defective, and one case, doubtful at first, but a certain case four years later.

It frequently happened that an original patient, diagnosed as having only suspicious symptoms, turned out to have relatives seriously affected.

George Ca., aged 42, after being operated on for cataract at Moorfields by Mr. Doggert and Mr. Lister, was found to have myotonia in the tongue and wasted thenars. Although he was only "suspicious," his mother had definite signs of the disease, and two of her brothers had had cataract for several years. One of these had a son definitely affected.

George had a brother Alfred, aged 38, the fourth in the sibship, who was defective and unmarried. On examination he complained of weakness and stiffness in his limbs, which had been present two to three years. He had a myopathic facies; the facial muscles were weak and there was suspicious myotonia in the tongue but nowhere else. The left thenar muscle was wasted laterally and his grip was weak. He was labelled "suspicious."

It seems likely that the mental defect as well as the other symptoms were the result of an affected genetic factor and that this case should not be counted as normal in this respect.

Still another family may be cited in which it would seem important to recognize certain members as being neither seriously affected nor again quite normal. It is best to consider them as *formes frustes,* or suspicious cases. In the family S., Dr. J. G. Greenfield described the following case in 1911.

Emma (Fam. No. 2), the eldest of this sibship, was normal in 1910, but in 1935, when she was 72, there was definite wasting in the lateral part of her thenars which may, however, have been the result of an injury. Facial weakness was considerable and she could not blow out her cheeks. There was suspicious myotonia in her tongue muscles too.

Alfred, the ninth of Dr. Greenfield's sibship, was normal in 1910, but in 1935 there was slight drooping of the eyelids, some facial weakness and myotonia in his tongue. Two years later he complained of stiffness in the upper and lower limbs, his temporals were somewhat wasted, as also his left sternomastoid and the arm

reflexes were not elicited, and there was considerable weakness of the dorsiflexors of the feet.

F. G. S., the youngest but one, was considered suspicious by Dr. Greenfield in 1910, but her condition was unchanged in 1935 and 1938.

A. S., the youngest, was normal in 1910 at the age of 25, but very severely affected in 1935, his illness having begun in 1917.

The existence of such suspicious cases is important in deciding whether the disease can skip a generation. For instance:—

Mrs. L. V. (Fam. No. 24) (described in *Brain* **60,** p. 516) had a deceased brother who had been severely affected and had been an in-patient at the National Hospital. Mrs. L. herself felt quite healthy. Her temporals, however, were slightly wasted and she was unable to blow out her cheeks. (No slit-lamp nor electrical examination done.) G. G. L., aged 26, her son, was definitely affected, as was proved by electric examination. He felt perfectly healthy.

An even more striking case was that of Frederick B. H. (Fam. No. 71), aged 53. He felt quite well and made no complaint of stiffness or weakness. His face, however, had a rather myopathic appearance and he was rather bald. His temporals were slightly wasted and there was suspicious weakness in blowing out his cheeks, and some myotonia in his tongue as well as his quadriceps, but no unmistakable sign of dystrophia myotonica.

Mrs. V., his sister, a case of Dr. Feiling, was severely affected.

Frederick B. H. had four children, and Dr. J. Clifford Richardson, Toronto, Canada, examined the second and third at Toronto and has kindly reported on them. They were affected by definite symptoms of the disease. The eldest had wasted temporals and complained of stiffness. She was labelled "suspicious." We found that the youngest of this sibship, a boy, was severely affected.

To sum up this section we would say that it is important to recognize that slight cases actually do exist in this disease. Recognition of such cases means that the incidence of the disease is much greater than 1:1, and this would make the hypothesis that the disease is transmitted by simple dominance impossible. Instances have been cited of normal cases having affected children, but in our series, such parents have always been suspicious cases. As already stated, we have therefore not found any case of a disease skipping a generation. It appears from the families quoted above that suspicious cases may either remain suspicious or may develop into a severe form of the disease. Whether environmental factors are of importance in this respect remains an open question.

Cases in which some cardinal symptoms was missing.—Ravin and Waring have said that the clinical picture in this disease is almost monotonous in the uniformity of its symptoms. If this were true, there would be more probability that the disease was transmitted by a single factor. If, however, it can be shown that in a considerable number of cases some cardinal symptom is missing, then this theory will not be so easy to main-

tain. We may perhaps be excused for describing in detail a number of families in which one or more members failed to show some cardinal symptom such as cataract, myotonia or wasting, while at the same time showing other symptoms. These cases at once suggest the possibility that the disease is transmitted by a number of factors, one for cataract, one for myotonia, one for wasting and the like. This question will then be discussed further.

(1) *Cases in which marked affection of muscles occurred in the absence of cataract.*—This occurrence is in fact not at all uncommon, although it has been held by some writers that the detection of cataract by slit-lamp examination is one of the earliest and most constant features of the disease (Waring, Ravin and Walker, 1940). A. Vogt (1931) also expressed doubt as to whether cases of dystrophia myotonica could be free from cataract. On the other hand, Fleischer (1918) and Baruch (1932), as well as Ravin and Waring (1939), reported definite cases of this disease in the absence of cataract.

The following are cases in which muscles were affected in the absence of cataract.

Case 1.—The propositus (Fam. No. 19) (Drs. E. Guttmann and A. Stokes, Maudsley Hospital), aged 26, had myotonic stiffness from infancy with mild but definite wasting in a few muscles. His brother, aged 23, and also his mother, aged 68, had definite myotonia and slight wasting, yet in none of these was cataract found by slit-lamp.

Case 2.—Albert B. (Fam. No. 18), a patient of Dr. Hinds Howell, St. Bartholomew's Hospital, aged 20, had marked myotonia and mild wasting, but no cataract (slit-lamp). Five brothers and two sisters were either definite or suspicious cases. None complained of dimness of vision. (No slit-lamp examination done.)

Case 3.—Sam L. (Fam. No. 46) (Dr. G. Riddoch, National Hospital), aged 52, had myotonia from infancy. Mild wasting, no dimness. Cataract not found with ophthalmoscope.

Case 4.—Karl S. (Fam. No. 12) had severe dystrophia myotonica with typical cataract. His son, aged 26, a low-grade defective, had definite myotonia, mild wasting and marked weakness in upper limbs, but no cataract (slit-lamp examination carried out twice at several months' interval).

Case 5.—Mrs. M. (Fam. No. 39), aged 51, was a definite case affected by typical myotonia, typical haggard face and neck muscles and weak dorsiflexors of the feet, but without cataract (slit-lamp). One of her brothers suffered from severe dystrophia myotonica.

Case 6.—Mrs. G. (Fam. No. 70), aged 31 (Dr. S. Westman), had no cataract (slit-lamp) but definite signs of the disease. She suffered from mild myotonia, slight weakness of facial muscles and her right supinator longus was smaller and weaker than the left one, although she was right-handed. Gripping was somewhat weak.

Case 7.—Mrs. H. (Fam. No. 44) (her sister was an in-patient at the National

Hospital under the late Dr. Collier), aged 47, had typical but mild myotonia, with wasted temporal muscles, and doubtful wasting of facial muscles, but no cataract (slit-lamp).

Case 8.—Catherine M. D. (Fam. No. 23), aged 26, had mild myotonia, confirmed by electrical examination, poor grip and slight wasting, but no cataract (slit-lamp). Her father was affected, judging from reports, while the latter's brother was a severe case of dystrophia myotonica in the National Hospital, Queen Square.

Case 9.—Anita R. (Fam. No. 25). A brother suffered from typical dystrophia myotonica with cataract. He was a patient of Dr. Purdon Martin. Myotonia was observed in her at 6 years and 10 months. Weakness in facial muscles appeared at 7 years, slight wasting in thenars at 9 years. She was free from cataract (slit-lamp examination) at the age of 8 and again at the age of 9 years and 6 months.

Case 10.—In the family Tho. (No. 9) (Dr. G. Riddoch) many brothers and sisters suffered from dystrophia myotonica, including cataract. Herbert Tho., aged 43, a cousin, as well as his father, had a wasted right sternomastoid (photo in *Brain*, **60**, 505), but no cataract (slit-lamp examination was carried out on Herbert).

Perhaps some critics, not convinced of the identity of myotonia congenita and dystrophia myotonica, which make the diagnosis "myotonia congenita" in the Cases 1, 2, 3 and 6, in spite of some wasting and weakness, but the diagnosis myotonia congenita is out of the question for the remaining cases.

(2) *Cases in which cataract appeared as an isolated symptom.*—A. Vogt and others have described cases in which cataract appeared in isolation in one generation, while dystrophia myotonica appeared in the next generation. We have also described such a case in *Brain*, **60**, 502.

The following two cases are examples of this.

Case 1.—Edgar C. (No. 36), aged 53, was a typical case of dystrophia myotonica, while his late father had had cataract. A sister of the late father, aged 75, had developed cataract at 57 years. She was free from muscle involvement when examined.

Case 2.—Mrs. Br. (Fam. No. 89), mentioned before, a case of Mr. E. Wolff (Royal Westminster Ophthalmic Hospital), was affected by typical symptoms of dystrophia myotonica. Mrs. R., her mother, 54 years, felt healthy and did not complain of her sight. We found no neurological abnormality in her, but Mr. Wolff observed a typical beginning cataract on slit-lamp examination.

Fearnsides (1915) examined a female with cataract and marked wasting of muscles. Many of her relatives had cataract. Myotonia, however, was not found in any one of this family.

The following case is of especial interest.

Case 3.—In the family Sm. (No. 2) a large sibship was affected by dystrophia myotonica (examined by J. G. Greenfield in 1911). A late sister of the father of this sibship was reported to have cataract. We have examined her two daughters, aged 60 and 67, as well as a son, aged 64. All three were affected by cataract, but were free from definite affection of muscle.

In this case there appears to be a tendency for the cataract to "breed true," thus favouring the hypothesis that it is transmitted by a separate factor. This will be discussed later.

(3) *Other cases without myotonia but with other symptoms of dystrophia myotonica.*—The following case is of interest as showing muscular wasting and idiocy in members of an affected family.

Case 1.—Mrs. Ca. (Fam. No. 1), together with many siblings and two daughters, suffered from dystrophia myotonica. Both her sons, aged 12 and 15, examined by Dr. R. G. Gordon and by one of us (A. S. P.) were idiots, affected by muscle wasting, especially of the sternomastoids. There was, however, no myotonia or cataract (Mr. Iles).

It seems likely that the following case showing wasting and cataract, but no definite myotonia, was really a case of the disease.

Case 2.—Albert Co., aged 37, a case of the late Dr. Collier, had weakness of the legs for three years. There was wasting and weakness in both quadriceps, hamstrings, right pectoralis and both brachio-radialis muscles. Facial muscles and sternomastoids were normal. There was no sign of myotonia. Electrical examination (Dr. L. D. Bailey) showed slow contraction at make and break of the galvanic current, doubtful hyper-excitability, but no definite sign of myotonia. Yet Mr. P. A. Williamson-Noble found typical cataract on slit-lamp examination. None of the patient's relatives were reported to be affected, although his father and two of three brothers, one of his sisters and one of his four children were examined.

Taylor (1923) observed a case of pseudo-hypertrophic myopathy in which there existed cataract similar to those found in dystrophia myotonica.

Verwey and Legras (1933) examined a family, some members of which had dystrophia myotonica, while others suffered from myopathy of Erb's type.

Cases without muscle wasting.—Cases in which myotonia appears early without much wasting or cataract, at least early in the disease, tend to run in certain families. For this reason a separate syndrome, myotonia congenita, has been described. As has been mentioned, Kinnier Wilson stated (1940) that wasting could occur in this syndrome. Yet Knaur (1936) has described a fertile family in which myotonia, in the absence of wasting, was associated with cataract in many members. One member, however, who was not examined, was perhaps affected by wasting.

Divry and Evrard (1936) also described similar cases.

The following is an example of this.

William Sm., aged 68 (Fam. No. 82), had typical myotonia in the hands and tongue and diminished arm reflexes, but no weakness or wasting of muscles. Cataract had been diagnosed six years previously. Alfred, his son, was a typical case of dystrophia myotonica, while Alfred's two brothers and one sister were also definitely affected.

The Significance of Incomplete Cases for the Theory of Multiple Factors.

Three different theories have been put forward regarding the mode of transmission of dystrophia myotonica.

We have already mentioned the first of these, which states that the disease is transmitted by simple dominance, that the proportion of affected to unaffected patients approaches 1 : 1, and that the disease is remarkably uniform in its clinical picture. Ravin and Waring are the most recent upholders of this view.

We believe, however, that this hypothesis is based on erroneous data. We have shown that the clinical picture is not uniform, but that cardinal symptoms such as myotonia, wasting and cataract may be absent. We have shown further that even when possible statistical fallacies are taken into consideration, the proportion of those definitely affected to normals is far more than 1 : 1.

The second view is that the disease is transmitted by a single factor, but that cases where some cardinal symptom is missing are to be explained by the operation of some modifying factor. The main objection to this theory is again that the proportion of affected to unaffected is so much greater than 1 : 1.

There remains the theory that the disease is transmitted by several factors, one being responsible for myotonia, one for wasting, one for cataract and so on. If this were so, we could explain the frequency of the disease being much in excess of that expected in simple dominance, as well as the absence of some cardinal symptom in certain members or groups of members of affected families.

On this view there are multiple independent factors present in an isolated state in the general population. These produce no effect, or only a mild effect when isolated, but a very marked effect when united (compare Ruggles Gates, 1929). In this way an affected sibship might result from apparently unaffected parents. Even if all the isolated factors were transmitted by recessive inheritance, it would still be possible for the factors in combination to be inherited by dominance, as "dominigenes" may change recessive inheritance into a dominant one (Goldschmidt, 1937, 1938).

We would remark at this point that we found no clear case of the disease suddenly appearing in a hitherto unaffected family. We were never sure, indeed, that we were dealing with even the second generation of the disease. There was a number of patients, however, like Case 1, p. 70,

Fam. No. 36, where the father had cataract and the son dystrophia myotonica. We had no records of the previous generation. Again, the Fam. By-Sc., No. 66, is of interest in this connection. The propositus, who was definitely affected, had had a brother who had died and had probably been affected. Both of the parents were married twice. The disease was probably inherited from the mother, because her sister had cataract. Yet the mother had a normal son (examined) by another man. The father had seven children by another woman. Two of these were normal on examination, while the other five were reported normal.

This case, in which parents had affected offspring of their own, but normal offspring by other partners suggests that the father must also have borne some defective factor which facilitated the appearance of the disease.

In another case, Fam. Ba., No. 61, Wm. Ba., aged 55, definitely affected, had a healthy daughter free from cataract by his first wife, but by his second wife, a daughter of 13 was affected and a son of 11 was an imbecile. It would appear, therefore, that the appearance of the disease is to some extent dependent on the apparently normal parent. We have not, however, been able to investigate this subject further.

Two objections may be brought against the theory of multiple factors. Firstly, if more than one factor were involved, we might expect to find more histories of consanguineous marriages. It is true that consanguinity was not very noticeable in our material (although there are three cases in Table II above). We were, however, dealing with patients resident in and around London, where intermarriage is not so frequent as in isolated localities. It seems likely that in many cases intermarriage had occurred before the families migrated to London, for we found very few cases where we were obviously dealing with the first or even with the second generation of the disease.

Henke and Seeger on the other hand, who were dealing with Black Forest peasants, reported many cases of intermarriage and also of the first affected generation of a family.

It has also been said that if multiple factors were involved, isolated symptoms would tend to "breed true," whereas the various symptoms of dystrophia myotonica tend to occur in combination.

We did in fact see cases like Case 3, Sm. (Fam. No. 2), where a woman from a myotonic family, who had cataract alone, as reported, had two daughters, each with cataract alone.

Also, myotonia in some affected families tends to persist from one generation to another with little manifestation of wasting or cataract. This

tendency of one symptom to "breed true" would seem to favour the hypothesis of multiple factors.

For all these reasons we believe that the theory that the disease is transmitted by multiple factors is the most satisfactory.

Progressive Deterioration and Regeneration in Families Affected by Dystrophia Myotonica.

The conception of degeneration is in no way a recent one. Blumenbach discussed degeneration in man as early as 1806.

Morel, the French psychiatrist (1857) maintained that progressive degeneration took place in families affected by mental disease, so that the members of subsequent generations became affected at an earlier age, until these families, having no offspring, eventually died out.

Morel, however, did not hold that this phenomenon always took place. It seems that his critics, e.g. Rádl (1930), often disregarded such sentences as (p. 324): "Nous désirons que ce mot 'fatalité' ne soit pas compris dans sa signification la plus absolue. Nous tenons à faire entrevoir dès ce moment que des circonstances favorables peuvent rompre cet enchaînement des faits pathologiques."

Darwin (1875) maintained that hereditary diseases appeared either at the same age as in the previous generation or at an earlier age and only rarely at a later age. He also quoted observations concerning anticipation reported by other authors (Lucas, Bowman).

Heilbronner (1903) reported anticipation in families affected by Huntington's chorea. Numerous writers agreed with Heilbronner and acknowledged "Heilbronner's law" (Henke and Seeger, 1927). Other writers, however, disagreed (Davenport and Muncey (1926), Falstein and Stone (1939), Kinnier Wilson (1940)).

Mott (1912) held that on an average mental patients became affected at an earlier age than their parents. Heron (1914) and Spencer Paterson (1933), however, demonstrated statistical fallacies in Mott's argument and concluded that Mott's findings were not sound.

Naegeli (1934) went so far as to say that the confused conception of degeneration should be given up completely. ("Den verschwommenen Begriff der Degeneration sollte man ganz aufgeben.")

In the case of dystrophia myotonica, however, severer symptoms, appearing to arise at an earlier age in subsequent generations, have been demonstrated (Fleischer (1922), Frey (1926), Henke and Seeger (1927)). Later Maas (1937), as well as Ravin and Waring (1939), published observations confirming this view.

Stern (1929), Kehrer (1936), Goldschmidt (1938) and Jonesco-Sisesti and Stroesco (1939) believed in the validity of progressive degeneration in families affected by dystrophia myotonica. This was, however, denied by Curtius (1939). We observed an apparent progression in the gravity of physical symptoms also in the numerous members of the additional thirty-seven families which we examined after the year 1937. Any condition which produces congenital mental defect will probably show progressive deterioration in subsequent generations. There is no doubt that the frequency of congenital mental defect in these families is a symptom of the disease just as much as, for instance, atrophy of the testicles. One of us (O. M.) has already mentioned forty cases of mental defect occurring in this disease.

Table VII shows that the vast majority of these defectives have one parent affected by dystrophia myotonica. It would appear that these cases of mental defect represent a true progressive degeneration. Otherwise we should expect to find some cases of mental defect in the first known generation of the disease. In fact, however, we never found any mental defective who definitely belonged to the first known generation affected by dystrophia myotonica. We only received a report of one case which was possibly a member of the first generation of the disease.

In family No. 67, X. Y., a scientist, though fit enough to carry on his occupation, submitted himself for examination and proved to be a mild case of the disease. He reported that his father was a definite but mild case. Three sisters of his father were probably affected also, and another, the youngest, was an idiot who died in infancy. One of the affected sisters of his father had seven children, several of whom were almost certainly affected. The youngest attended a special school. As there was no report of the grandparents, the idiot, who was a sister of the father, perhaps belonged to the first affected generation.

The Problem of Regeneration.

Besides the families in which members of the second and third generation became affected by more severe symptoms and at an earlier age, we also examined families in whom members of subsequent generations were less affected than those of the preceding ones.

Mrs. Do. (Fam. No. 2) belonged to a family examined by Greenfield (1911). She was a suspicious case at that time, and she was in the same state of health in 1935. Her daughter was perfectly healthy when we examined her at the age of 13 in 1935 and again at the age of 16 in 1938.

In the family Ba. (No. 61), Wil. Ba., a man of 55, was a very severe case, as also both his children from the second wife, a girl of 13 and a mentally defective boy of 11, whereas his first wife's daughter, a married woman of 26, was perfectly healthy. She was also free from cataract as shown by slit-lamp examination.

In the family Ma. (a case of Dr. Carmichael—No. 28) the father as well as

THE PROBLEM OF PROGRESSIVE DETERIORATION IN SIBLINGS.

Darwin (1875) cited an observation of Bowman to the effect that " when cataract affects several members of the family in the same generation, it is often seen to commence at the same age in each, e.g. in one family several infants or young persons may suffer from it; in another several persons of middle age."

Penrose (1932) has shown that certain forms of mental defect seem to occur at the end of the family. O. Maas (1933) showed in a small series of achondroplasic dwarfs that the affected sib was generally the last or last but one.

Spencer Paterson (1933) discussed the statistical fallacies which have beset this problem.

Fraser Roberts (1940) said in his " Introduction to Medical Genetics ": " Some fœtal malformations become more frequent as maternal age advances, e.g. anencephaly and congenital heart disease. Presumably the effect of advanced maternal age on the ordinary child is a very slight one or is perhaps non-existent, but if the child possesses the gene or genes which reduce the margin of safety the effects of otherwise unimportant differences may become manifest."

The problem of progressive deterioration in sibships has been discussed also in dystrophia myotonica. Fleischer (1918) said that dystrophia myotonica started in members of one generation at about the same time of life and he called this homochronous heredity.

Maas (1937) published material in favour of fraternal anticipation. Ravin and Waring (1939) also described it in dystrophia myotonica. " Although this phenomenon does not appear to be as regular in its occurrence as generational anticipation, it is strikingly evident in many of the sibships reported."

The accompanying Tables IX and X show severe cases of dystrophia myotonica occurring more frequently in later-born siblings than among the first-born, while Table XI gives figures for defectives.

The value of this table becomes enhanced by considering that the penetrative power of dystrophia myotonica usually is much greater in the male than in the female. This fact has to be considered in sibship No. 7 in which the patient was the second, whilst suspicious younger sibs were females. The same considerations apply to sibship No. 14, in which, also, the youngest was a female, and to sibship No. 16 in which the youngest was also a female.

We have also to consider that the younger sibs often were still fairly young and not severely affected at the time of examination, but might

three sons were severe cases, but one son of 24 and a daughter of 22 felt perfectly healthy. Except mild atrophy of the temporals, no abnormal symptoms were observed. There was no cataract (slit-lamp).

TABLE VII.—CONGENITAL MENTAL DEFECTIVES.

Affection of parents by dystrophia myotonica.

I. *Affection of the father confirmed by examination.*

(1) G. R.	(Family No. 1)	(5) F. B.	(Family No. 29)
(2) G. S.	(,, ,, 2)	(6) G. B.	(,, ,, 50)
(3) W. S.	(,, ,, 12)	(7) D. W. B.	(,, ,, 61)
(4) E. F. De	(,, ,, 13)	(8) N.	(,, ,, 77)

II. *Affection of the grandfather confirmed by examination.*

(1) R. B. (Family No. 50)

III. *Affection of the father reported.*

(1) C. B.	(Family No. 32)	(3) M. F.	(Family No. 48)
(2) E. C.	(,, ,, 37)	(4) W. K.	(,, ,, 52)

IV. *Affection of the late father probable as step-sister* (from the same father) also suffers from dystrophia myotonica.

(1) R. J. M. (Family No. 7)

V. *Affection of the mother confirmed by examination.*

(1) O. E. J.	(Family No. 1)	(10) T. W. C.	(Family No. 20)
(2) D. C.	(,, ,, 1)	(11) P. L. P	(,, ,, 59)
(3) B. C.	(,, ,, 1)	(12) W.	(,, ,, 60)
(4) B. J. C.	(,, ,, 1)	(13) A. S.	(,, ,, 72)
(5) F. D.	(,, ,, 6)	(14) J. C.	(,, ,, 75)
(6) K. R.	(,, ,, 8)	(15) E. C. H.	(,, ,, 86)
(7) L. W.	(,, ,, 7)	(16) E. C.	(,, ,, 86)
(8) D. R.	(,, ,, 4)	(17) F. C.	(,, ,, 86)
(9) W. T.	(,, ,, 11)	(18) E. C.	(,, ,, 86)

VI. *Affection of the mother reported.*

(1) M.A.G.	(Family No. 88)	(2) Y. (Family No. 67)

VII. *Affection of the mother probable.*

(1) C. G.	(Family No. 5)	(3) A. C. (Family No. 76)
(2) M. C.	(,, ,, 15)	

VIII. *Insufficient report on parent.*

(1) F. G.	(Family No. 17)	(3) H. B.	(Family No. 67)
(2) A. B.	(,, ,, 57)	(4) Z.	(,, ,, 67)

We found also in other families normal or suspicious individuals who were the descendants of a severely affected patient (*see* Table VIII). It is obviously impossible to foretell whether these healthy or suspicious persons will remain in good health for a further period, and if they will have healthy descendants.

But these observations make it probable that progressive degeneration does not take place in every case.

It seems that progressive deterioration is a more frequent event than regeneration in dystrophia myotonica, even when we take into consideration all possible statistical fallacies. Examination of our pedigrees favours the assumption that at least a certain number of families affected by dystrophia myotonica become extinct, but our result does not demonstrate how often extinction or regeneration takes place.

become severe cases later on. In sibship No. 15 the four youngest were only 21, 18, 15 and 13 years of age. The occurrence of deterioration at a more advanced age has been proved by sibship No. 2. (The youngest was unaffected when examined in 1911 by Dr. Greenfield but a severe case in 1935.) The fact that a severe case is not the youngest in his sibship may result also from an acute disease of this sib in childhood. In sibship No. 43 the severe case was the fourth of those whom we examined. He had suffered from sunstroke when 7 years of age. He was delirious at that time for a whole week. It seems not unlikely that in consequence of this illness which damaged the central nervous system, the symptoms of dystrophia myotonica became aggravated and therefore became manifest at an earlier age.

For our examination of fraternal deterioration we used one of Fisher's statistical methods (1938).

Table XII divides all the cases into six groups, N (normal), U2 (alive not examined), U1 (deceased, not examined), S (suspicious), A1 (of moderate severity), A2 (severe).

The left-hand columns show the total number of individuals in each birth rank, while the right-hand columns show the numbers that would be expected to occur in each birth rank if this depended on chance alone. (*See* Fisher's Statistical Methods, p. 26.)

This table shows a slight tendency for later-born sibs to be more seriously affected than the earlier born. This is all the more surprising because we would expect in the case of a progressive disease that the older sibs would be more seriously affected. If this age difference were adjusted (e.g. by dealing with complete generations), the degree to which the later-born were affected would be much more marked.

Such a table which deals with a disease that usually becomes severe in the third or fourth decade of life is not so reliable as one which deals with a disease such as congenital mental defect which is manifest in the earliest years.

A striking result is obtained when we compare the number of members of each group who were last born with those who were expected. Thus for normals , 4 were last born when 4·33 were expected; for slightly affected there were 21, while 21·69 were expected; for the moderately affected there were 18 as against 21·16 expected. In all these cases there was no significant difference. When, however, we come to the seriously affected, we find that 43 were last born while only 27·4 were expected, an increase of 58 per cent. In the case of mental defectives, 17 out of 31 were last born, whilst only

TABLE VIII.—REGENERATION IN DYSTROPHIA MYOTONICA.

Cases where descendants of severe cases are unaffected, suspicious or mild.

A.—*Father a severe case.*

	Name	*No. of family*	*Issue*				
1	Wa.	68	(1) F. severe 39	(2) F. susp. 37	(3) F. susp. 35	(4) M. susp. 31	
2	Dy.	43	(1) Died inf.	(2) Died inf.	(3) F. susp. 21		
3	Bai.	50	(1) M. Myoton in tongue. Seldom shaved. Healthy in every other respect 31	(2) M. severe 29	(3) to (10) Miscarriages		
4	Dra.	5	(1) M. severe 22	(2) F. mild 19	(3) M. susp. 14	(4) M. susp. 11	(3) & (4) are children fromsecond wife

B.—*Mother a severe case.*

	Name	*No. of family*	*Issue*				
1	Da.	6	(1) F. very mild 28	(2) F. susp. 26	(3) Mis.	(4) Mis.	
2	Wh.	7	(1) F. susp. 22	(2) F. severe 17	(3) Mis.	(4) Mis.	(5) M. severe 13
3	Si.	78	(1) F. susp. 23				
4	St.	79	(1) F. susp. 20				
5	Co.	75	1st to 6th & 9th not seen (4th, 5th, 6th died in infancy, 1st, 2nd, 3rd and 9th reported healthy)		(7) M. susp. 29	(8) M. severe 26	(1) F. susp. 22 (11) F. susp. 18

C.—*Father with mild definite muscle symptoms and typical cataract.*

Name	*No. of family*	*Issue*			
Bo.	58	(1) M. mild 35	(2) M. severe 31	(3) F. susp. 30	(4) F. susp. 22

D.—*Mother with mild definite muscle symptoms and typical cataract.*

	Name	*No. of family*	*Issue*				
1	Br.	89	(1) M. healthy 12				
2	Be.	8	(1) F. mild 29	(2) F. norm. 21	(3) M. norm. 25	(4) M. norm. 23	(5) M. severe 21
3	De.	6	(1) M. susp. 39	(2) M. susp. 37	(3) Died inf.	(4) Mis.	(5) M. mild 34
			(6) M. susp. 31	(7) Died inf.	(8, 9) Mis.	(10) F. mild 24	(11) M. severe 19

E.—*Father affected by typical myot. in tongue (not examined by slit-lamp). His brother a severe case.*

Name	*No. of family*	*Issue*		
Dr.	5	(1) F. not seen	(2) M. sl. susp. 17	(3) F. susp. 15

(M = male, F = female. The figure below the sibs gives the age when examined.)

TABLE IX.—DYSTROPHIA MYOTONICA IN SIBSHIPS IN WHOM THREE OR MORE SIBS WERE EXAMINED.

Signs: X not examined (miscarriage, dead, abroad).
N = normal, S = suspicious, A_1 = mild affection.
A_2 = severe affection, + = female.

No. in this table	*Name*	*No. of the family in our collection*	*No. of sibs in this sibship*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	A.Wo.	3	19	X	X	X	X	X	X	X	X	X	X	X	X	X	X	S	S	S	X	A_2
2	Ma.	41	16	X	X	X	S	S	X	A_2	X	S	X	X	X	X	X	X	X			
3	Sm.	2	15	+S	A_1	X	+X	+S	+A	A_2	X	+A_1	+A_2	+A_1	+A_2	+A_2	+S	A_2					
4	Dy.	43	14	X	+A_1	X	+A_1	X	X	X	+A_1	X	A_2	+S	S	X	X						
5	Ca.	20	13	X	X	X	X	S	X	X	X	X	X	A_1	X	+A_2							
6	Gil.	88	12	A_2	X	X	X	+A_1	X	X	X	+A_1	S	X	+A_2								
7	Co.	75	11	X	X	X	X	X	X	S	A_2	X	+S	+S									
8	De.	6	11	S	S	X	X	A_1	S	X	X	X	+A	A_2									
9	Dev.	13	11	X	+S	X	X	X	X	X	X	+S	A_2	A_2									
10	Ho.	83	10	X	X	X	+S	X	X	A_1	A_1	+A_2	X										
11	Sho.	27	10	X	A_1	S	X	+A_1	S	S	X	A_1	A_2										
12	Tho.	9	9	X	+A_1	A_1	A_1	+A_1	X	X	A_2	+A_2											
13	Bov.	63	9	A_1	X	X	X	X	A_1	A_1	X	A_2											
14	Re.	1	9	A_1	+S	+S	A_2	+A_2	+A_2	+A_1	A_2	+S											
15	Re. II.	1	9	A_2	X	+A_1	X	+A_2	A_1	A_1	A_1	A_1											
16	Se.	12	9	X	X	N	A_2	+A_2	X	X	X	+N											

TABLE X.—SEVERE PHYSICAL SYMPTOMS OF DYSTROPHIA MYOTONICA IN SIBSHIPS IN WHOM THREE OR MORE SIBS WERE EXAMINED.

Not examined sibs disregarded.

Numbers in this Table and in Table IX	*Name*	*Numbers of the family in our collection*	*Number of examined sibs*	*Severe affection*
1	A.Wo.	3	4	The 4th
2	Ma.	41	4	,, 3rd
3	Sm.	2	12	,, 5th, 7th, 9th, 10th, 12th
4	Dy.	43	6	,, 4th
5	Ca.	20	3	,, 3rd
6	Gi.	88	6	,, 1st and 6th
7	Co.	75	4	,, 2nd
8	De.	6	6	,, 6th
9	Dev.	13	4	,, 3rd and 4th
10	Ho.	83	4	,, 4th
11	Sh.	27	7	,, 7th
12	Tho.	9	6	,, 5th and 6th
13	Bv.	63	4	,, 4th
14	Ro.	1	9	,, 4th, 5th, 6th, 8th
15	Re. II	1	7	,, 1st and 3rd
16	Se.	12	4	,, 2nd and 3rd

TABLE XI.—DYSTROPHIA MYOTONICA.

Congenital Mental Defectives.

Birth Rank	*Number of Cases in each Birth Rank*	
	Expected	*Actual*
1	6·05	2
2	6·05	6
3	5·55	3
4	4·55	3
5	3·55	5
6	2·15	6
7	1·32	1
8	0·74	3
9	0·62	1
10	0·17	0
11	0·17	0
12	0·08	1
Total	31·00	31

The middle column shows how many patients would be expected in each birth rank, if that depended on chance alone. The last column shows how many were actually born in each birth rank. The table shows that in the first four birth ranks only 14 were born when 22·10 were expected, but in birth ranks 5—12, 17 were born when only 8·90 were expected. The later born are therefore relatively more likely to be defective than the earlier born.

TABLE XII.—BIRTH RANK.

Dystrophia myotonica (1941).

Birth Rank	N		U1		U2		S		A1		A2		Total	
	Tot.	*Exp.*	*Tot.*	*Exp.*	*Tot.*	*Exp.*	*Tot.*	*Exp.*	*Tot.*	*Exp.*	*Tot.*	*Exp.*	*Tot.*	*Exp.*
1	3	4·38	11	10·16	43	37·77	15	21·69	28	21·26	23	27·40	123	122·66
2	4	4·38	11	10·16	44	37·77	23	21·69	17	21·26	25	27·40	124	122·66
3	5	2·88	6	8·73	42	37·77	22	19·19	19	17·26	16	22·90	110	108·73
4	4	2·55	9	8·40	33	34·40	17	15·86	11	16·26	21	18·57	95	96·04
5	0	1·80	6	6·90	28	29·65	16	12·36	13	13·26	15	14·07	78	78·04
6	2	0·80	6	5·90	20	24·25	8	9·36	11	9·26	12	9·47	59	59·04
7	0	0·80	7	4·73	16	17·58	4	5·85	7	6·59	7	5·80	41	41·35
8	0	0·51	2	3·73	17	13·44	3	5·15	7	5·73	4	4·66	33	33·22
9	1	0·39	2	2·23	8	12·31	5	3·25	6	3·73	3	3·28	25	25·19
10	0	0·17	2	1·79	7	8·31	2	2·81	0	1·96	4	1·61	15	16·65
11	0	0·17	0	1·59	7	6·61	3	2·11	1	1·16	3	1·31	14	12·95
12	0	0·17	1	0·59	3	4·24	2	1·29	0	0·98	2	0·76	8	8·03
13	0	0·17	2	0·34	1	2·66	0	0·79	0	0·48	2	0·59	5	5·03
14	0	0·17	1	0·26	2	1·96	1	0·63	0	0·48	0	0·51	4	4·01
15	0	0·17	0	0·11	1	1·60	1	0·48	0	0·27	1	0·44	3	3·07
16	0	0·11	0	0·11	1	1·47	1	0·28	0	0·00	0	0·11	2	2·08
17	1	0·11	0	0·11	0	0·73	0	0·05	0	0·00	0	0·05	1	1·05
18	0	0·11	0	0·11	1	0·73	0	0·05	0	0·00	0	0·05	1	1·05
19	0	0·11	0	0·11	0	0·73	0	0·05	0	0·00	1	0·05	1	1·05
Total	20	19·95	66	66·06	274	273·98	123	122·94	120	119·94	139	139·03	742	741·90

Incidence of dystrophia myotonica in relation to place in family (birth rank). It is possible to state by special statistical procedure how many members of affected families would occur in each birth rank, if the birth rank (1st, 2nd, 3rd, &c.) depended on chance alone. In the table above these expected numbers are given in the second column (headed "Exp.") in each case, while the total numbers actually found are given in the first column headed "Tot."

N=normal, U1=patient dead, unknown if affected, U2=patient alive, unknown if affected, S=suspicious for the disease or slightly affected, A1=moderately affected, and A2= grossly affected.

Note.—As in Table V, only those sibships are included which contain at least one definite case of the disease. Suspicious and normal children of affected parents are omitted, where no sib is affected.

6·20 were expected: that is about three times as many as expected (compare Table XI).

To sum up, we would say that there is definite evidence that younger members of a sibship become more severely affected than the older members. This fact may be interpreted in different ways. It may be that the germ-plasm is directly affected, or that environmental factors such as undernourishment in younger members of large families affect the disease. Perhaps also the father's age and other causes from the father's side may play a part in the frequent severer affection of younger sibs.

Our results concerning dystrophia myotonica are in accordance with Roberts' view on progressive deterioration in sibships.

Conclusion and an Apology.

In conclusion we would say that more pressing work in the past two years has made it impossible for us to analyse our material to a greater extent. We should have liked, for instance, to have investigated the following points in detail: The exact frequency of individual symptoms; whether parent and child pairs and whether sib pairs tend to conform in their symptoms; the significance of half-sibs for the mode of transmission; the mortality associated with individual symptoms; and lastly the incidence of particular symptoms in the two sexes.

We have thought it advisable, however, to publish the present findings, although incomplete, because they seem more reliable than conclusions based on smaller material which has been published in recent years. We are confident that a fuller analysis of our material in more leisured times will bear out our present conclusions.

Summary.

(1) The present study of the familial aspects of dystrophia myotonica is based on an analysis of members of 94 affected families. For reasons given in a previous paper we believe that dystrophia myotonica is essentially the same disease as myotonia congenita and paramyotonia.

(2) We believe that the disease is more frequent than is generally supposed. In the families of the 94 propositi, 261 individuals showed definite signs of the disease, while another 285 were affected by suspicious symptoms.

(3) Although the disease is frequently noticed for the first time in the third and fourth decades of life we have observed it in cases aged 14, 12, 9, 8, 6, 5, 4 and 3.

(4) Although patients generally die by the age of 50 we have occasionally found one comparatively well beyond the ages of 60 and 70.

(5) With regard to fertility, in certain families in which for the most part symptoms were only slight, members were often remarkably prolific. Such families are generally of low intelligence. Mental defect, however, and other symptoms affecting earning power, combined with atrophy of the testes, specifically causing impotence, caused a marked fall in the number of children in later generations.

(6) There was a high incidence of miscarriage and infantile mortality, which was probably due specifically to the disease process and not merely to the low social status of the families affected.

(7) Twinning appears to be particularly frequent and this may be related to a noxa affecting the germ plasm.

(8) Although patients are occasionally found of high social status (the present series includes a writer and artist, both of wide repute), most families are low in the social scale. The mental defect and mental enfeeblement are not the result of their low social status, but rather the cause of the progressive descent of certain families in the social scale.

(9) Although the opposite was sometimes found, it was more frequent for severe cases to be of the male sex, and milder cases to be females.

(10) The disease is transmitted in a dominant manner. In twenty families one member was markedly affected in both the first and second generation, while in others even more generations were affected by definite signs. In several cases stepbrothers and stepsisters were affected.

(11) No indisputable case has been found of the disease skipping a generation.

(12) The disease is inherited from affected male and female with equal frequency.

(13) The question is discussed whether the disease is transmitted as a dominant through one single factor. Objections to this view are brought forward. Henke and Seeger's findings, which seemed to uphold the unifactorial hypothesis, were based on small numbers and hearsay evidence. In our series the proportion of those definitely affected to those unaffected is much more than 1 : 1. In considering the hereditary aspects of disease, it is necessary to recognize a class of patients with mild or " suspicious " symptoms who are different from normals. Examples are given. The existence of these makes the proportion of affected to unaffected still higher. Cases are described of incomplete syndromes in which some cardinal symptom such as myotonia, wasting or cataract is missing. A case—one of several—is quoted of cataract separating out and " breeding true." There was also evidence, where a patient married twice, that the disease affected one sibship more than the other. Consanguinity is probably not

infrequent in early generations. The last two points will be specially investigated at a later date. The conclusion is reached that multiple factors are involved, which are recessive in isolation, but dominant when united.

(14) There is evidence that in many families the disease comes on at an earlier age and in a more intense form in successive generations, even when allowance is made for possible statistical errors. Congenital mental defect, which is part of the disease process, contributes to this result. Mental defect was found in the first known generation of the disease only in one case, but was not at all rare in the second or subsequent examined generations.

There were certain families in which the opposite process, that of regeneration, appeared to take place. This, however, was a rarer phenomenon.

(15) It was also usual for younger members of a sibship to develop the disease at an earlier age than the older siblings and in a more severe form. Cases that were seriously affected, and those with mental defect, occurred with remarkable frequency among the youngest born of a sibship.

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Notices of Recent Publications.

Encephalitis: A Clinical Study. By J. B. Neal and collaborators. London: H. K. Lewis. 1942. Pp. 563. Price 42s.

At a time when interest is increasing in the various forms of acute encephalitis, this comprehensive summary will be welcome to the neurologist and neuropathologist. Although entitled a clinical study, the volume deals with epidemiology, ætiology, pathology and bacteriology as well as with the relevant symptom complexes. Indeed, in some ways the purely clinical chapters are the least satisfactory in that they contain catalogues of all the symptoms recorded by all observers, but do not attempt to place before the reader any vivid picture of the illnesses and their behaviour.

As is common in summaries of the kind, the reader is not given any adequate clues to the probable value of the many statements and opinions cited. To learn that someone has expressed the view that disseminated sclerosis is a virus disease is not useful unless some indication is given, either of the grounds upon which the view is based, or of the absence of a factual foundation for it. Too many guesses of this kind find a place in the pages of this book. Those cases of polyneuritis associated with a high protein content in the cerebrospinal fluid are given a short chapter under the superfluous eponym of the "Guillain-Barré syndrome," but how they come to find themselves mentioned in a work on encephalitis is not clear; presumably, again, because someone has speculated that they also may express the action of some unknown neurotropic virus.

But these are minor defects, and the volume will be found very useful as a work of reference on the important subject of which it treats.

Aids to the Investigation of Peripheral Nerve Injuries. M.R.C. War Memorandum No. 7. H.M. Stationery Office, 1942. Price 2s.

In 1920 the Medical Research Council published a monograph (Special Report Series No. 54) on the diagnosis and treatment of peripheral nerve injuries with 60 pages of text and 18 illustrations. This provided a concise, yet comprehensive, guide to the various clinical features of peripheral nerve injuries, their morbid anatomy and their treatment.

The present successor of this monograph sets itself a somewhat more modest task, as its title indicates. It is an atlas of some technically excellent photographs designed to show how the normal actions of muscles in the limbs may be elicited and assessed, together with some diagrams of the peripheral limb nerves and their motor distribution, of the areas of sensory loss resulting from nerve lesions and of the axial lines and spinal segmental sensory distribution.

Despite the excellence of the photographs, it is doubtful if the monograph will be as useful to those for whom it is intended as was its predecessor, for the introductory page and a half of text cannot be called "an aid to investigation," and the photographs do not show the characteristic deformities or atrophies characteristic of peripheral nerve injuries. Even the normal movements are not always adequately

illustrated. For example, the reader is given no indication of the role of the lower trapezius in maintaining the normal position of the scapula, and is not told that some winging of the scapula may ensue from paralysis of this muscle, or how to distinguish this winging from that following paralysis of serratus anterior. Winging from weakness of serratus is best seen when the advanced arm, pressing against resistance, is below the horizontal, that from weakness of lower trapezius when the arm is above the horizontal. The actions of the rhomboids and spinati are inadequately shown, while to speak of the "belly" of gastrocnemius, soleus and deltoid in the singular is inaccurate.

The statement found in the legends to many of the photographs that "the muscle belly can be felt and sometimes seen" is unsatisfactory in that in the muscular subjects in whom the great majority of peripheral nerve injuries are encountered the bellies of subcutaneous muscles can be seen when in contraction.

The anatomist will not agree with the segmental innervation given to some of the muscles, e.g. C4 to the rhomboids and spinati, for this root does not innervate any of the upper limb muscles, while the axial lines given in figs. 73 and 74 are not accurate.

A concise statement of the main features, motor, sensory and trophic, of the different peripheral nerve palsies would have added immeasurably to the value of the photographs, and the need is not met by the scanty legends provided. In short, while the authors have provided an attractive atlas of photographs that should be of some help to medical officers in assessing muscular actions, they have not perhaps risen to the height of their opportunity or justified the title of the monograph.

Roentgen Treatment of the Nervous System. By C. G. Dyke and L. M. Davidoff. Henry Kimpton, London, 1942. Pp. 194. Price 15s.

This careful, critically written and fully documented monograph is a welcome addition to neurological literature. The responsiveness of all varieties of intracranial and spinal tumour is fully discussed and details of dosage given. The role of radiation in infective, inflammatory, degenerative and other diseases is also considered. It is rare to find a monograph devoted exclusively to therapy so judicially written, and thus such positive claims as the authors make inspire the greater confidence. The neurologist and the neurosurgeon alike will find this little book of great usefulness.